Attachment A

Article

Double-Blind, Placebo-Controlled Comparison of Imipramine and Paroxetine in the Treatment of Bipolar Depression

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Objective: This study compared the efficacy and safety of paroxetine and imipramine with that of placebo in the treatment of bipolar depression in adult outpatients stabilized on a regimen of lithium.

Method: In a double-blind, placebo-controlled study, 117 outpatients with DSM-III-R bipolar disorder, depressive phase, were randomly assigned to treatment with paroxetine (N=35), imipramine (N=39), or placebo (N=43) for 10 weeks. In addition to lithium monotherapy, patients may have received either carbamazepine or valproate in combination with lithium for control of manic symptoms. Patients were stratified on the basis of trough serum lithium levels determined at the screening visit (high: >0.8 meq/liter; low: ≤0.8 meq/liter). Primary efficacy was assessed by change from baseline in scores on the Hamilton Rating Scale for Depression and the Clinical Global Impression illness severity scale.

Results: Differences in overall efficacy among the three groups were not statistically significant. For patients with high serum lithium levels, antidepressant response at endpoint also did not significantly differ from placebo. However, both paroxetine and imipramine were superior to placebo for patients with low serum lithium levels. Compared to imipramine, paroxetine resulted in a lower incidence of adverse events, most notably emergence of manic symptoms.

Conclusions: Antidepressants may not be useful adjunctive therapy for bipolar depressed patients with high serum lithium levels. However, antidepressant therapy may be beneficial for patients who cannot tolerate high serum lithium levels or who have symptoms that are refractory to the antidepressant effects of lithium.

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The treatment of bipolar depression represents a clinical challenge, and appropriate treatment strategies remain more anecdotal than data-based. There is an extensive literature guiding treatment of patients with unipolar depression, but treatment of bipolar depression has not been extensively studied, and effective treatments are not well-defined (1, 2). Lithium is considered standard mood-stabilizing therapy for bipolar disorder (3–6). However, up to 50% of patients effectively maintained with lithium therapy may be unresponsive to its antidepressant effects (4, 7). When lithium monotherapy is not effective in managing depression or if patients are unable to tolerate the side effects of high serum lithium levels, patients with bipolar disorder may require combination therapy with antidepressants (3).

Monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, bupropion, and the selective serotonin reuptake inhibitors (SSRIs) have been evaluated for treatment of the depressive component of bipolar disorder (2, 3, 6, 8, 9). In a comparison of imipramine and tranylcypromine in depressed patients with bipolar disorder, the rate of response (defined as an endpoint Clinical Global Impression [CGI] score ≥ 2 or 3) to imipramine was 48%, and the response rate for tranylcypromine exceeded 80% (10). However, Prien et al. (11) noted that combined imipramine/lithium therapy offered no advantage over lithium alone in the treatment of bipolar depression. Additional clinical trials have demonstrated that the tricyclic antidepressants have a rate of response (defined as ≥50% improvement in score from baseline on the Hamilton Rating Scale for Depression) between 50% and 70% in the treatment of bipolar depression (10, 12–14). Bupropion was as effective as desipramine in one double-blind comparative study (14). Only a limited number of trials have evaluated the effectiveness of SSRIs in the treatment of bipolar depression (13, 15, 16). Cohn et al. (13) reported that bipolar patients treated with fluoxetine had a significantly greater response rate than those treated with imipramine. In a 6-week, double-blind comparison of paroxetine and amitriptyline in lithium-stabilized patients with breakthrough major depression, Bauer et al. (15) reported significantly greater responses (as determined by Hamilton depression scale and CGI severity of illness scores) in paroxetine-treated patients.

Although MAOIs appear to be effective in treating bipolar depression, safety issues and dietary restrictions often

limit their use in general clinical practice. Therapy with tricyclic antidepressants is also associated with a high incidence of adverse events, and many patients are unable to tolerate the anticholinergic side effects (13). Both tricyclic antidepressants and MAOIs have a low therapeutic index, which is a major concern in patients with bipolar disorder because of their high rate of suicide attempts. The SSRIs have a lower incidence of adverse events, particularly anticholinergic and cardiac effects (17, 18). Thus, the safety profile of SSRIs may offer an advantage over tricyclic antidepressants and MAOIs and may increase patient compliance.

The potential for the so-called switch into mania is another risk that must be considered when initiating antidepressant therapy in patients with bipolar depression (19–22). In one analysis, induction of mania occurred in 3.7% of 242 bipolar patients treated with SSRIs and in 11.2% of 125 patients treated with tricyclic antidepressants (20). Bupropion was reported as having induced mania in one small, open-label series (23). However, other investigators have reported that, when added to lithium, thyroxine, or anticonvulsant regimens, bupropion is not associated with mania in rapidly cycling patients (24) and is less likely to induce mania than desipramine (14).

In order to address some of the unresolved issues regarding the treatment of bipolar depression, we compared the efficacy and safety of paroxetine and imipramine with that of placebo in the treatment of bipolar depression in adult outpatients stabilized with lithium therapy.

Method

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled study that was conducted to assess the efficacy and safety of paroxetine and imipramine in combination with lithium therapy in the treatment of bipolar depression. Outpatients with bipolar disorder who were currently in a major depressive episode were enrolled. A 1-week, single-blind, placebo period was used to screen potential patients for inclusion in the study.

Diagnostic procedures included conducting a DSM-III-R multiaxial evaluation, physical examination, psychiatric and medical history, routine laboratory analyses, and pregnancy test; performing an ECG and vital signs assessment; measurement of serum trough lithium level and body weight; and administration of the 21-item version of the Hamilton depression scale (25) and the CGI severity of illness scale. Following the psychiatric and medical screening examination, eligible patients were stratified into two groups on the basis of whether their trough serum lithium level at the screening visit was low (≤0.8 meq/liter) or high (>0.8 meq/liter) and then were randomly assigned to one of the three treatment groups.

Patients randomly assigned to paroxetine treatment received 20 mg/day for the first 3 weeks; thereafter, dose increases of 10 mg/day were permitted every 7 days up to a maximum dose of 50 mg/day. Patients receiving imipramine began at a dose of 50 mg/day with a forced titration to 150 mg/day at the rate of 50 mg every 7 days over the first 3 weeks of the study. After this titration period, imipramine dose increases of 50 mg/day were permitted every 7 days up to a maximum dose of 300 mg/day. Dose reduction was permitted once if necessary for adverse events; retitration to the original dose level was allowed if the adverse event remitted. Following the 10-week treatment phase, patients were gradually tapered off all study medications.

The study was approved by the institutional review board at each of the 19 participating centers, and each patient provided written informed consent before entry into the study.

Patient Selection

All patients enrolled in the study fulfilled DSM-III-R criteria for bipolar disorder and scored ≥15 on the 21-item version of the Hamilton depression scale at both the screening and baseline evaluations. The total Hamilton depression scale score could not have decreased by more than 25% between the screening and baseline evaluations. Eligible patients experienced at least one previous episode of mania or major depression within the past 5 years and had been maintained on a regimen of lithium alone or in combination with sodium valproate or carbamazepine for at least 7 weeks before the screening visit. Serum lithium levels were between 0.5 and 1.2 meq/liter (0.4 meq/liter for patients intolerant to lithium) for at least 6 weeks before the screening evaluation. Serum lithium concentrations were measured 1 week after initiation of study medication and remained within prior defined levels for all eligible patients. Lithium dose adjustments were not allowed unless serum levels deviated beyond the 0.5–1.2 meq/liter range (0.4 meq/liter for lithium intolerance), in which case doses were adjusted to maintain levels within the permitted range. Patients were at least 18 years old.

Patients who met DSM-III-R criteria for bipolar disorder but who were not currently depressed were excluded, as were patients who required therapy with both sodium valproate and carbamazepine or those who had been diagnosed with an axis I disorder other than bipolar disorder as the primary disorder within 6 months of the screening, including dysthymia and bipolar II disorder. Patients who were rapid cyclers (four or more manic/hypomanic or depressive episodes within 12 months of the baseline evaluation), who had experienced recent manic/hypomanic episodes within 4 weeks of baseline, or who were prone to spontaneous remission (depressive episodes of no more than 8 weeks' duration) were excluded. Additional exclusion criteria were any serious medical disorder or condition, such as cardiovascular disease or history of narrow-angle glaucoma, that would preclude the administration of tricyclic antidepressant therapy; concomitant therapy with other psychotropic drugs, not including chloral hydrate; and concomitant therapy with warfarin, cardiac glycosides, phenytoin, cimetidine, type 1C antiarrhythmic agents, quinidine, sulfonylurea derivatives, or tryptophan. Patients who met the DSM-III-R criteria for substance abuse within 3 months of the study or the criteria for substance dependence within 6 months of the study were ineligible. Patients who were judged by the investigator to be at serious suicidal or homicidal risk were also excluded from the study.

Assessment

During the 10-week study period, patients were assessed for both efficacy and adverse events at baseline and at weeks 1–6, 8, and 10. Laboratory evaluations and an ECG were performed at the screening visit and at weeks 4 and 10. Baseline laboratory evaluations were only performed if abnormal values were noted at the screening visit.

Primary efficacy parameters were mean change from baseline in the total score on the first 17 items of the Hamilton depression scale and mean change from baseline in score on the CGI severity of illness scale. Clinical response parameters included the proportion of patients achieving Hamilton depression scale scores ≤7 and the proportion of patients with CGI global improvement scores ≤2. These parameters are clinically accepted as indicative of therapeutic response.

TABLE 1. Baseline Ratings on Depression Measures for 117 Outpatients With Bipolar Depression Randomly Assigned to Treatment With Paroxetine, Imipramine, or Placebo and Changes in Scores After 10 Weeks

	Paroxetine				Imipramine				Placebo			
	Baseline		Change		Baseline		Change		Baseline		Change	
Group and Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total[a]												
Hamilton depression scale	20.38	3.91	–10.2	7.30	20.71	3.90	–10.1	7.26	21.57	3.87	–8.06	7.28
CGI severity of illness scale	4.21	0.69	–1.33	1.38	4.31	0.66	–1.28	1.38	4.33	0.66	–0.91	1.38
Patients with high serum lithium levels[b]												
Hamilton depression scale	20.29	3.78	–9.79	7.11	21.35	3.75	–9.35	7.09	21.95	3.76	–10.4	7.10
CGI severity of illness scale	4.21	0.60	–1.14	1.42	4.35	0.62	–0.94	1.44	4.29	0.60	–1.24	1.42
Patients with low serum lithium levels[c]												
Hamilton depression scale	20.37	4.01	–10.4	7.28	20.11	4.01	–10.7	7.28	21.18	3.99	–5.82	7.32
CGI severity of illness scale	4.21	0.74	–1.47	1.35	4.26	0.74	–1.58	1.35	4.36	0.75	–0.59	1.36

[a] Data set from the intent-to-treat population. Paroxetine group, N=33; imipramine group, N=36; placebo group, N=43.
[b] Serum lithium level at screening examination >0.8 meq/liter. Paroxetine group, N=14; imipramine group, N=17; placebo group, N=21.
[c] Serum lithium level at screening examination ≤0.8 meq/liter. Paroxetine group, N=19; imipramine group, N=19; placebo group, N=22.

Safety evaluations were based on routine adverse event monitoring, vital sign assessments, and a hypomania/mania assessment based on DSM-III-R criteria. Patients were asked a nonleading question at each postbaseline assessment, such as "Do you feel differently in any way since starting this treatment?" Positive responses were investigated and documented on the case report form. These evaluations, as well as body weight determinations, were evaluated at each visit. The effect of paroxetine and imipramine on serum lithium concentrations was monitored by obtaining blood samples at weeks 2, 4, 6, and 10. Adverse events were elicited by asking the patient nonleading questions.

Data Analysis

Data are presented from the intent-to-treat population. The endpoint data set was the primary time point of interest and was determined for each patient from the last available observation while receiving treatment. The group was stratified on the basis of serum lithium level at the screening examination (high: >0.8 meq/liter, low: ≤0.8 meq/liter). Lithium stratification criteria were determined a priori. The proportion of patients achieving dichotomous response was analyzed by the Cochran-Mantel-Haenszel test adjusting for lithium stratification or by Fisher's exact test. The chi-square test was used for analyses within lithium strata. Change from baseline score, defined as score minus baseline score, of efficacy scales was assessed by parametric analysis of variance. The study was designed to enroll 35 patients per arm, which would allow 70% power to detect a 5-point difference on the Hamilton depression scale score (SD=8.5) between treatment groups.

The primary comparison of interest was between the paroxetine and placebo treatment groups regardless of lithium stratification. Because all other statistical comparisons were considered to be secondary, no adjustments for multiple comparisons were made. Therefore, the achievement of statistical significance for the primary efficacy variables at endpoint (i.e., changes from baseline in scores on the Hamilton depression scale and CGI severity of illness scale) was set at $p \leq 0.05$.

The general linear model procedure of SAS (Cary, N.C.) was used to perform the analysis with a model that included effects for treatment and lithium strata for scores on the Hamilton depression scale (first 17 items) and CGI severity of illness scale. Analyses of all other efficacy variables were performed with a model that included only an effect for treatment. Additional analyses were performed within lithium strata that included only the treatment effect. Type III sums of squares were used. The analyses were designed to include an investigator effect; however, 14 of the 19 investigational sites had fewer than eight total patients. Thus, no analyses with an investigator effect were performed. The treatment-by-lithium strata interaction was found to be nonsignificant and was not included in the model. Because only a small number of patients experienced manic and hypomanic episodes, these episodes were not analyzed.

All statistical tests were two-tailed. Tests of hypothesis of interactions were made at the 10% significance level, and all other tests were made at the 5% significance level. Data are presented as means and standard deviations. The CONTRAST statement from the general linear model procedure of SAS was used for treatment group comparisons. Interaction assessments were conducted as per protocol. However, significant interactions were not found and therefore not presented.

Results

Demographic and Clinical Characteristics

A total of 117 outpatients were enrolled by 19 centers: 35 patients (mean age=42.5 years, range=24–66) were randomly assigned to the paroxetine group, 39 (mean age=41.9 years, range=21–71) received imipramine, and 43 (mean age=40.4 years, range=21–66) were given placebo. The paroxetine, imipramine, and placebo groups were similar in age, gender (54.3%, 59.0%, and 53.5%, respectively, were female), race (97.1%, 100.0%, and 90.7%, respectively, were Caucasian), and cardiac history. Concomitant medications were used by 82.9% (N=29) of the patients in the paroxetine treatment group, 76.9% (N=30) of the patients in the imipramine group, and 81.4% (N=35) of the patients in the placebo group. The prevalence of concomitant use of valproic acid was similar for the paroxetine (11.4%, N=4) and placebo (9.3%, N=4) groups and was much less for the imipramine group (2.6%, N=1); only one patient each from the paroxetine (2.9%) and imipramine (2.6%) groups received carbamazepine during the study. Because of the small number of patients receiving concomitant therapy with these agents, no influence on overall efficacy in the treatment groups could be determined.

Mean daily doses at study endpoint (i.e., the last available observation for each patient while receiving treatment) were 32.6 mg for paroxetine (range=20–50 mg) and 166.7 mg for imipramine (range=50–300 mg). At endpoint, five imipramine-treated patients were receiving

Comparison of Change Values					
Paroxetine Versus Placebo		Imipramine Versus Placebo		Paroxetine Versus Imipramine	
F (df=1, 108)	p	F (df=1, 108)	p	F (df=1, 108)	p
1.67	0.20	1.52	0.22	0.01	0.94
1.70	0.20	1.37	0.25	0.02	0.88
F (df=1, 49)	p	F (df=1, 49)	p	F (df=1, 49)	p
0.06	0.81	0.20	0.66	0.03	0.87
0.04	0.85	0.40	0.53	0.15	0.70
F (df=1, 57)	p	F (df=1, 57)	p	F (df=1, 57)	p
4.06	0.05	4.53	0.04	0.01	0.92
4.41	0.04	5.52	0.03	0.06	0.81

doses lower than the minimum 150 mg/day required by the protocol.

Efficacy

Mean changes in score on the Hamilton depression scale and CGI severity of illness scale from baseline to endpoint for the paroxetine and imipramine groups were not significantly different than those of the placebo-treated group (Table 1). A high placebo response rate also occurred in the high serum lithium level group, with no statistical separation from placebo for either paroxetine or imipramine. However, among the low serum lithium level patients, paroxetine and imipramine were superior to placebo in terms of mean change from baseline in scores on the Hamilton depression scale and CGI severity of illness scale (Table 1).

Therapeutic response was defined as Hamilton depression scale score ≤7 or CGI global improvement score ≤2. For the total intent-to-treat population, there were no statistically significant differences in response rates among those receiving paroxetine, imipramine, or placebo (per Hamilton criterion: 45.5% [N=15], 38.9%, [N=14], and 34.9% [N=15], respectively; per CGI criterion: 54.5% [N=18], 58.3% [N=21]; and 46.5% [N=20]). Among the study completers, Hamilton depression scale scores ≤7 were achieved by 56.0% (N=14 of 25) of the paroxetine-treated patients, 47.8% (N=11 of 23) of the imipramine-treated patients, and 53.8% (N=14 of 26) of the placebo-treated patients. Similarly, CGI global improvement scores ≤2 were achieved by 68.0% (N=17) of the paroxetine-treated patients, 73.9% (N=17) of the imipramine-treated patients, and 69.2% (N=18) of the placebo-treated patients.

Among patients with high serum lithium levels, similar response rates were noted among those receiving paroxetine, imipramine, or placebo (per Hamilton criterion: 35.7% [N=5], 41.2%, [N=7], and 38.1% [N=8], respectively; per CGI criterion: 57.1% [N=8], 47.1% [N=8]; and 52.4% [N=11]). For those with low serum lithium levels, no statistically significant differences in response rates were seen among those receiving paroxetine, imipramine, or placebo (per Hamilton criterion: 52.6% [N=10], 36.8%, [N=7], and 31.8% [N=7], respectively; per CGI criterion: 52.6% [N=10], 68.4% [N=13]; and 40.9% [N=9]).

There were five patients whose endpoint imipramine dose did not reach 150 mg/day. Each of these patients withdrew from the study before reaching the 150-mg dose level at week 3 (two were receiving 50 mg/day, and three were receiving 100 mg/day). The duration of therapy for these patients ranged from 5 to 14 days. In four of these patients, the Hamilton depression scale score decreased 1 to 18 points; in one patient (who was receiving 50 mg/day), the Hamilton depression scale score increased 2 points.

Emergent Adverse Events

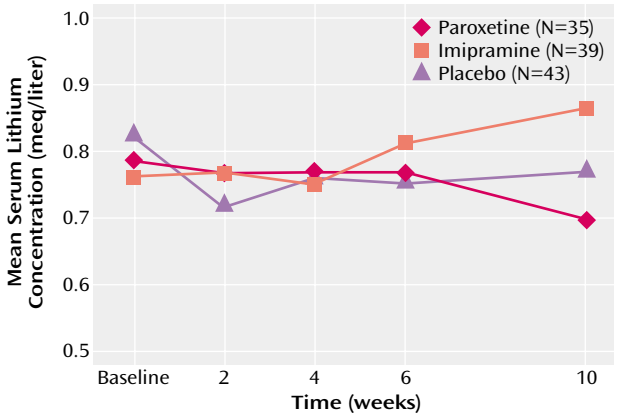
Treatment-emergent adverse events were determined by asking open-ended, nonleading questions. Tremor (40.0%, N=14), insomnia (37.1%, N=13), and somnolence (34.3%, N=12) were the most frequently reported effects of the paroxetine-treated patients. For the patients in the imipramine group, dry mouth (61.5%, N=24), tremor (38.5%, N=15), and headache (41.0%, N=16) were noted most commonly. In the placebo group, headache (39.5%, N=17), somnolence (25.6%, N=11), and insomnia (23.3%, N=10) were the most frequently occurring adverse events, with tremor occurring in 9.3% (N=4) of the patients. Patients treated with imipramine reported a higher incidence of abnormal ejaculation (18.8%) and impotence (25.0%) than did patients receiving paroxetine (0.0% and 6.3%, respectively) or placebo (5.0% and 0.0%, respectively).

Adverse events precipitated study discontinuation in one paroxetine patient (2.9%), 12 imipramine patients (30.8%), and five placebo patients (11.6%). Other reasons for withdrawal from the study included lack of efficacy (paroxetine: 2.9% [N=1]; imipramine: 2.6% [N=1]; placebo: 18.6% [N=8]), deviation from protocol (including noncompliance) (5.7% [N=2], 5.1% [N=2], and 2.3% [N=1], respectively), and subjects lost to follow-up (17.1% [N=6], 2.6% [N=1], and 4.7% [N=2]).

No serious adverse events were reported in the paroxetine group. Two patients in the imipramine group (5.1%) and four patients in the placebo group (9.3%) experienced serious adverse events. In the imipramine group, one patient was hospitalized for mania on study day 42, and another patient developed physical aggression with homicidal ideation and was withdrawn from the study on day 29. Of the four placebo-treated patients experiencing serious adverse events, two were hospitalized for manic episodes (not necessarily protocol-defined mania), one developed increased depression with paranoid hallucinations and delusions, and the fourth did not complete the taper phase and developed reemergence of depression. The adverse events associated with active treatment were consistent with the safety profiles for SSRIs and tricyclic antidepressants.

By definition, participating patients did not meet the DSM-III-R criteria for hypomania or mania at the screen-

FIGURE 1. Mean Serum Lithium Concentrations of 117 Outpatients With Bipolar Depression Randomly Assigned to 10 Weeks of Treatment With Paroxetine, Imipramine, or Placebo



ing or baseline examination. Endpoint analysis revealed that no patient treated with paroxetine experienced induction to mania. However, three patients (7.7%) treated with imipramine and one patient (2.3%) treated with placebo experienced treatment-emergent mania. Among the three patients treated with imipramine who experienced mania, two were from the low serum lithium level group. The placebo-treated patient who developed mania was in the low serum lithium level group.

Lithium concentrations remained within the therapeutic range for all patients treated with paroxetine or imipramine (Figure 1). There was no evidence that either paroxetine or imipramine influenced lithium pharmacokinetics. Weight gain was observed in three patients (7.7%) treated with imipramine and in three patients (7.0%) in the placebo group. Four patients treated with paroxetine experienced a change in weight: two (5.7%) gained weight, and two (5.7%) lost weight.

Discussion

To our knowledge, this is the largest study to evaluate an SSRI for the treatment of bipolar depression and the first controlled clinical trial to assess the efficacy and safety of paroxetine treatment for this disorder. For both the total patient population and among those with high serum lithium levels, neither paroxetine nor imipramine were distinguishable from placebo. However, in the endpoint analysis, patients with low serum lithium levels who were treated with paroxetine or imipramine demonstrated significant improvement compared to those treated with placebo.

Although our study was not designed to measure the antidepressant effects of lithium, when lithium stratification groups were compared, it could be inferred from the data that the antidepressant effects of lithium were more prominent in patients with high serum lithium levels. The antidepressant effects of high serum lithium levels are not surprising in view of the considerable literature suggesting an antidepressant effect of lithium in bipolar depression and to a lesser extent in unipolar depression and depression associated with schizoaffective disorder (6, 26–28).

Clinical response parameters for the endpoint analysis and the completer analysis were a Hamilton depression scale score ≤7 or a CGI global improvement scale score ≤2. Overall, in the clinical response analyses, we observed no statistically significant differences for the treatment groups. This lack of statistical difference may be associated with the relatively small patient population and the high placebo response rate in these lithium-treated patients. Tondo et al. (29) reported in an open study of 26 patients with bipolar disorder that fluoxetine was effective in treating depressive episodes. It is of interest that the mean serum lithium level for those patients was 0.57 meq/liter, well within the range of our low serum lithium level group.

Paroxetine was well-tolerated in these patients. Adverse events led to withdrawal from the study for one patient (2.9%) in the paroxetine group compared with 12 patients (30.8%) in the imipramine group. These findings are consistent with other reports of adverse events during SSRI therapy (12, 17, 30).

Resting tremor was noted by 40.0%, 38.5%, and 9.3% of the patients treated with paroxetine, imipramine, and placebo, respectively. Psychopharmacologically active drugs, including tricyclic antidepressants and SSRIs, may exacerbate existing lithium-related tremor (15, 31, 32). Although baseline tremor was not assessed, making it impossible to determine the causal relationship of paroxetine or imipramine, tremor was likely associated with lithium inasmuch as similar rates of tremor have been reported in patients with bipolar disorder maintained on a regimen of lithium alone (31–33). The high incidence of anticholinergic adverse reactions and tremor has also been reported in previous studies that evaluated imipramine alone and imipramine and lithium combination therapy (11, 12).

Imipramine-treated patients voluntarily reported a higher incidence of abnormal ejaculation (18.8%) and impotence (25.0%) than did paroxetine-treated patients. In clinical trials evaluating paroxetine for the treatment of unipolar depression, sexual dysfunction was reported in 6%–33% of patients (34, 35). In our study, the incidence of abnormal ejaculation and impotence was 0% and 6.3%, respectively, in paroxetine-treated patients.

There is considerable evidence supporting the association of antidepressants and the induction of mania and rapid cycling in patients with bipolar disorder (19–22, 36). Paroxetine did not precipitate a switch to mania in any patient, whereas the incidence of mania in imipramine-treated patients was 5.9% and 10.5% among the high and low serum lithium level groups, respectively. Among the total patient population, 7.7% of patients receiving imipramine and 2.3% of patients in the placebo group developed mania. It should be noted, however, that concomitant use of valproic acid was more common in the

paroxetine and placebo groups than in the imipramine group. This is consistent with previous studies that also have shown a high propensity for imipramine to cause mania (10, 11, 37). In a review of other similar clinical trials (20), tricyclic antidepressants (11.2%) were much more likely to induce a switch to mania in patients with bipolar depression than were placebo (4.2%) or SSRIs (3.7%) (SSRIs versus tricyclic antidepressants, $p<0.01$).

In evaluating the effect of paroxetine and imipramine on serum lithium levels, lithium concentrations remained within the accepted therapeutic range throughout the course of the study. No treatment-emergent adverse events were attributed to lithium toxicity. These results are consistent with previous studies that evaluated the effects of concomitant imipramine (11, 37) and paroxetine (38) on lithium levels in patients with bipolar disorder. Thus, the lack of effect by paroxetine and imipramine on lithium toxicity minimizes additional safety concerns regarding the use of lithium with these agents.

Several limitations of our study must be considered. The high response rate in the placebo group and the small sample sizes may have limited our ability to detect statistical differences between treatment groups. All patients in the paroxetine group were taking therapeutic daily doses of paroxetine (20 to 50 mg), but five patients in the imipramine group (12.8%) were receiving daily doses of 50 mg or 100 mg, which are at the lower end of the therapeutic range for this antidepressant. Previous studies indicate that as many as one-half of patients receiving lithium may respond to the antidepressant effects of this agent (4, 7). Furthermore, carbamazepine may be useful in the treatment of refractory depression (39). Thus, all patients in this study were receiving medication (i.e., lithium and, in a small number of patients, carbamazepine or valproate) capable of improving scores on the depression efficacy scales. It is unlikely that the low rate of concomitant carbamazepine or valproate use in this study influenced overall outcome. However, it is noteworthy that an antidepressant effect was evident in patients in the total patient population analysis, as well as among those with high serum lithium levels. Yet in those patients receiving active drug who had low lithium serum levels, a pronounced therapeutic effect was demonstrated with imipramine and paroxetine, and significant differences from placebo were seen.

The results of this study indicate that patients with bipolar depression who maintain high serum lithium levels may not require additional antidepressant medications. However, patients with low serum lithium levels or those who cannot tolerate high serum lithium levels may benefit from augmentation therapy with either paroxetine or imipramine. These findings suggest the need for additional studies of antidepressant treatment of bipolar depression, particularly in patients stabilized on a regimen of lithium.

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Received Mar. 12, 1999; revisions received May 24 and Dec. 1, 2000; accepted Jan. 6, 2001. From the Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine. Address reprint requests to Dr. Nemeroff, Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, 1639 Pierce Dr., Suite 4000, Atlanta, GA 30322.

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References

1. Kalin NH: Management of the depressive component of bipolar disorder. Depress Anxiety 1996/1997; 4:190–198
2. Zornberg GL, Pope HG: Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993; 13:397–408
3. Gelenberg AJ, Hopkins HS: Report on efficacy of treatments for bipolar disorder. Psychopharmacol Bull 1993; 29:447–456
4. Sachs GS: Treatment-resistant bipolar depression. Psychiatr Clin North Am 1996; 19:215–236
5. Schou M: Forty years of lithium treatment. Arch Gen Psychiatry 1997; 54:9–13
6. Srisurapanont M, Yatham LN, Zis AP: Treatment of acute bipolar depression: a review of the literature. Can J Psychiatry 1995; 40:533–544
7. Gershon S, Soares JC: Current therapeutic profile of lithium. Arch Gen Psychiatry 1997; 54:16–20
8. Angst J, Stabl M: Efficacy of moclobemide in different patient groups: a meta-analysis of studies. Psychopharmacology (Berl) 1992; 106:S109–S113
9. Dantzler A, Salzman C: Treatment of bipolar depression. Psychiatr Serv 1995; 46:229–230
10. Himmelhoch JM, Thase ME, Mallinger AG, Houck P: Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 1991; 148:910–916
11. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Arch Gen Psychiatry 1984; 41:1096–1104

12. Baumhackl U, Bizière K, Fischbach R, Geretsegger CH, Hebenstreit G, Radmayr E, Stabl M: Efficacy and tolerability of moclobemide compared with imipramine in depressive disorder (DSM-III): an Austrian double-blind, multicentre study. Br J Psychiatry 1989; 155(suppl 6):78–83
13. Cohn JB, Collins G, Ashbrook E, Wernicke JF: A comparison of fluoxetine, imipramine, and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 1989; 4:313–322
14. Sachs GS, Lafer B, Stoll AL, Banov M, Thibault AB, Tohen M, Rosenbaum JF: A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994; 55: 391–393
15. Bauer M, Zaninelli R, Muller-Oerlinghausen B, Meister W: Paroxetine and amitriptyline augmentation of lithium in the treatment of major depression: a double-blind study. J Clin Psychopharmacol 1999; 19:164–171
16. Simpson SG, DePaulo JR: Fluoxetine treatment of bipolar II depression. J Clin Psychopharmacol 1991; 11:52–54
17. Kasper S, Lepine JP, Mendlewicz J, Montgomery SA, Rush AJ Jr: Efficacy, safety, and indications for tricyclic and newer antidepressants. Depression 1994/1995; 2:127–137
18. Sheline YI, Freedland KE, Carney RM: How safe are serotonin reuptake inhibitors for depression in patients with coronary heart disease? Am J Med 1997; 102:54–59
19. Dilsaver SC, Swann AC: Mixed mania: apparent induction by a tricyclic antidepressant in five consecutively treated patients with bipolar depression. Biol Psychiatry 1995; 37:60–62
20. Peet M: Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994; 164:549–550
21. Stoll AL, Mayer PV, Kolbrener M, Goldstein E, Suplit B, Lucier J, Cohen BM, Tohen M: Antidepressant-associated mania: a controlled comparison with spontaneous mania. Am J Psychiatry 1994; 151:1642–1645
22. Wehr TA, Goodwin FK: Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 1979; 36:555–559
23. Fogelson DL, Bystritsky A, Pasnau R: Bupropion in the treatment of bipolar disorders: the same old story? J Clin Psychiatry 1992; 53:443–446
24. Haykal RF, Akiskal HS: Bupropion as a promising approach to rapid cycling bipolar II patients. J Clin Psychiatry 1990; 51:450–455
25. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
26. Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Muller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T: Comparative efficacy of lithium and amitriptyline in the maintenance treatment of recurrent unipolar depression: a randomised study. J Affect Disord 1996; 40:179–190
27. Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Muller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T: Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: a randomised study. Eur Arch Psychiatry Clin Neurosci 1997; 247: 42–50
28. Greil W, Ludwig-Mayerhofer W, Erazo N, Schochlin C, Schmidt S, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T: Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: a randomised study. J Affect Disord 1997; 43: 151–161
29. Tondo L, Mannu P, Silvetti F, Altamura C: Fluoxetine augmentation in bipolar disorder patients on maintenance lithium treatment. Int J Psychiatry Clin Pract 1997; 1:203–206
30. Cohn JB, Wilcox CS: Paroxetine in major depression: a double-blind trial with imipramine and placebo. J Clin Psychiatry 1992; 53(suppl):52–56
31. Gelenberg AJ, Jefferson JW: Lithium tremor. J Clin Psychiatry 1995; 56:283–287
32. Vestergaard P, Poulstrup I, Schou M: Prospective studies on a lithium cohort, III: tremor, weight gain, diarrhea, psychological complaints. Acta Psychiatr Scand 1988; 78:434–444
33. Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, Lavelle J: Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989; 321:1489–1493
34. Battegay R, Hager M, Rauchfleisch U: Double-blind comparative study of paroxetine and amitriptyline in depressed patients of a university psychiatric outpatient clinic (pilot study). Neuropsychobiology 1985; 13:31–37
35. Dunbar GC, Cohn JB, Fabre LF, Feighner JP, Fieve RR, Mendels J, Shrivastava RK: A comparison of paroxetine, imipramine, and placebo in depressed out-patients. Br J Psychiatry 1991; 159: 394–398
36. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L: Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995; 152:1130–1138
37. Quitkin FM, Kane J, Rifkin A, Ramos-Lorenzi JR, Nayak DV: Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. Arch Gen Psychiatry 1981; 38:902–907
38. Haenen J, De Bleeker E, Mertens C, Batholome F, Pardoen D, Stellamans G, Leyman S, Schotte G: An interaction study of paroxetine on lithium plasma levels in depressed patients stabilised on lithium therapy. Eur J Clin Res 1995; 7:161–167
39. Post RM, Uhde TW: Carbamazepine as a treatment for refractory depressive illness and rapid cycling manic-depressive illness, in Treating Resistant Depression. Edited by Zohar JH, Belmaker RH. New York, PMS, 1987, pp 175–235

Attachment B

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From Massachusetts General Hospital, Harvard Medical School (GSS, AAN, MJO), and Boston University (MWO) — all in Boston; Case Western Reserve University–University Hospitals Case Medical Center, Cleveland (JRC); Bay- lor College of Medicine and South Cen- tral **...**
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Suicide risk in bipolar disorder during treatment with lithium and divalproex
FK Goodwin, B Fireman, GE Simon... - JAMA: the journal of ..., 2003 - Am Med Assoc
Corresponding Author and Reprints: Frederick K. Goodwin, MD, George Washington University Medical Center, Department of Psychiatry, 2150 Pennsylvania Ave NW, Washington, DC 20037 (e-mail: fgoodwin@mfa.gwu.edu). **...** Context Several studies have suggested that lithium **...**
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Antidepressants for bipolar depression: a systematic review of randomized, controlled trials
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OBJECTIVE: This study reviewed the evidence from randomized, controlled trials on the efficacy and safety of antidepressants in the short-term treatment of bipolar depression. METHOD: The authors performed a systematic review and meta-analysis of randomized, controlled trials. **...**
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Treatment and prevention of depression
[PDF] from psychologicalscience.orgSD Hollon, ME Thase... - Psychological Science in ..., 2002 - psi.sagepub.com
Summary—Depression is one of the most common and de- bilitating psychiatric disorders and is a leading cause of sui- cide. Most people who become depressed will have multiple episodes, and some depressions are chronic. Persons with bi- polar disorder will also **...**
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Efficacy of quetiapine monotherapy in bipolar I and II depression: a double-blind, placebo-controlled study (the BOLDER II study)
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The 2002 American Psychiatric Association (APA) guidelines for the treatment of bipolar disorder recommended more conservative use of antidepressants. This change in comparison with previous APA guidelines has been criticized, especially from some groups in Europe. The Munich **...**
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Bipolar disorder
[PDF] from univaq.itB Müller-Oerlinghausen, A Berghöfer... - The Lancet, 2002 - Elsevier
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Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up
[HTML] from psychiatryonline.orgL Altshuler, T Suppes, D Black... - American Journal of ..., 2003 - Am Psychiatric Assoc
OBJECTIVE: While guidelines for treating patients with bipolar depression recommend discontinuing antidepressants within 6 months after remission, few studies have assessed the implications of this strategy on the risk for depressive relapse. This study examined the effect of **...**
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Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression
[HTML] from psychiatryonline.orgJF Goldberg, KE Burdick... - American Journal of ..., 2004 - Am Psychiatric Assoc
OBJECTIVE: Previous studies suggest that the dopamine agonist pramipexole may possess antidepressant properties. The authors conducted a preliminary randomized, placebo-controlled trial to determine the safety and antidepressant efficacy of pramipexole in **...**
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Topiramate versus Bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study
RS McIntyre, DA Mancini, S McCann... - Bipolar ..., 2002 - Wiley Online Library
Results: The percentage of patients meeting a priori response criteria (≥50% decrease from baseline in mean HDRS-17 total score) was significant for both topiramate (56%) and bupropion SR (59%) [t(17)=2.542, p=0.04 and t(17)=2.661, p=0.03, respectively]. Baseline **...**
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[PDF] **The Texas implementation of medication algorithms: update to the algorithms for treatment of bipolar I disorder**
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Received Dec. 29, 2004; accepted April 20, 2005. From the Department of Psychiatry, the University of Texas Southwestern Medical Center, Dallas (Dr. Suppes); the Department of Psychological Science, Purdue University, West Lafayette, Ind. (Dr. Dennehy); the Department of **...**
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OBJECTIVE: Antidepressant responses were compared in DSM-IV bipolar and unipolar depression. METHOD: The authors analyzed clinical records for outcomes of antidepressant trials for 41 patients with bipolar depression and 37 with unipolar depression, similar in **...**
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Antidepressant-induced mania: an overview of current controversies
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OBJECTIVE: Clinicians have few evidence-based options for the management of treatment-resistant bipolar depression. This study represents the first randomized trial of competing options for treatment-resistant bipolar depression and assesses the effectiveness and safety of **...**
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World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of bipolar disorders, part I: treatment of bipolar depression
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Results A total of 174 adults with bipolar disorder I, II or not otherwise specified, currently in the depressed phase, were included. All three antidepressants were associated with a similar range of acute response (49-53%) and remission (34-41%). There was a significantly increased **...**
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[BOOK] **Structured group psychotherapy for bipolar disorder: The life goals program**
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Mark S. Bauer, MD, is in the Department of Psychiatry and Human Behavior at Brown University and on staff in the Mental Health Service of the Department of Veterans Affairs Medical Center in Providence, RI. Dr. Bauer's career-long focus has been on improving outcome in **...**
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Practice guideline for the treatment of patients with bipolar disorder (revision)
R Hirschfeld, CL Bowden, MJ Gitlin, PE Keck… - Focus, 2003 - Am Psychiatric Assoc
A. Psychiatric management At this time, there is no cure for bipolar disorder; however, treatment can decrease the associated morbidity and mortality [I]. Initially, the psychiatrist should perform a diagnostic evaluation and assess the patient's safety and level of functioning to arrive at **...**
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A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression
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OBJECTIVE: Modafinil is approved by the US Food and Drug Administration for improving wakefulness in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea, and shift-work sleep disorder. This study was conducted to evaluate the efficacy and safety of **...**
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Treatment options for bipolar depression and treatment-resistant unipolar depression include aug- mentation of antidepressant therapy with a nonantidepressant drug, including atypical antipsychotics. Risperidone is effective in combination with fluvoxamine, paroxetine, or **...**
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Clinical consequences of under-recognized bipolar spectrum disorder
DL Dunner - Bipolar disorders, 2003 - Wiley Online Library
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OBJECTIVE: Practice guidelines have advised against treating patients with antidepressants during bipolar mixed states or dysphoric manias. However, few studies have examined the outcomes of patients with co-occurring manic and depressive symptoms who are treated with **...**
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[PDF] **Risperidone and paroxetine given singly and in combination for bipolar depression.**
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Received July 15, 2003; accepted June 9, 2004. From the Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn. (Dr. Shelton); and Neuroscience Education Institute, Carlsbad, Calif. (Dr. Stahl). This study was supported by a grant from Janssen **...**
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Dept. of Psychiatry of Weill Medical College of Cornell University; University of Pennsylvania (RCY); the Dept. of Psychiatry, Bipolar Disorders Program (LG); Western Psychiatric Institute and Clinic, Dept. of Psychiatry, Univ. of Pittsburgh School of Medicine and the Geriatric **...**
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Estimates of the lifetime prevalence of bipolar disorder from two major community surveys of the general population of the United States indicate that 1.0% to 1.6% of adults and 1.2% of children and adolescents (age 9 to 17 years) are affected by this illness. 38 and 59 Data from **...**
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Advances in the pharmacologic treatment of bipolar depression
PE Keck - Biological psychiatry, 2003 - Elsevier
The pharmacologic treatment of bipolar depression has not been well studied in randomized, controlled trials. Thus important clinical questions regarding the efficacy in bipolar depression of mood stabilizers, antidepressants, and new antiepileptic and atypical **...**
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The treatment of bipolar depression
GS Sachs, CL Koslow… - Bipolar disorders, 2000 - Wiley Online Library
Misdiagnosis and mistreatment of bipolar depression may lead to dramatic consequences, but treatment of the depressed phase of the disorder is remarkably understudied. Conceptually, bipolar depression is a diagnosis given to patients with a current episode of major **...**
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Antidepressant properties of anticonvulsant drugs for bipolar disorder
CL Ernst… - Journal of clinical psychopharmacology, 2003 - journals.lww.com
A growing number of anticonvulsant drugs are receiving attention as possible mood stabilizers. This attention is based mainly on the assumption that the antimanic efficacy of anticonvulsants makes them suitable as mood stabilizers. However, their antidepressant properties have **...**
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OBJECTIVE: Little is known about how often bipolar depressive episodes are accompanied by subsyndromal manic symptoms in bipolar I and II disorders. The authors sought to determine the frequency and clinical correlates of manic symptoms during episodes of bipolar **...**
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ECNP consensus meeting. Bipolar depression. Nice, March 2007
[HTML] from europeanneuropsychopharmacology.comGM Goodwin, I Anderson, C Arango… - European …, 2008 - Elsevier
DSM-IV, specifically its text revision DSM-IV-TR, remains the preferred diagnostic system. When employed in general population samples, prevalence estimates of bipolar disorder are relatively consistent across studies in Europe and USA. In community studies, first onset of bipolar **...**
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Conceptualizing changes in behavior in intervention research: the range of possible changes model.
[HTML] from nih.govA De Los Reyes… - Psychological Review, 2006 - psycnet.apa.org
An international movement has focused on identifying evidence-based interventions that were developed to change psychological constructs and that are supported by controlled studies. However, inconsistent findings within individual intervention studies and among multiple **...**
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A review of acute treatments for bipolar depression
PH Silverstone… - International clinical …, 2004 - journals.lww.com
Bipolar patients generally spend much more time in the depressed phase of their illness than the manic phase, and there are many more bipolar type II and bipolar spectrum disorder patients than there are bipolar type I. Additionally, there is a significant risk of suicide in bipolar **...**
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9 Pharmacological Treatments for Unipolar Depression Charles B. Nemeroff Alan F. Schatzberg The treatment of unipolar major depression with antidepressant medication is well established on the basis of scores of randomized placebo-controlled trials involving thousands of **...**
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Current guidelines for the treatment of bipolar type II (BP II) major depressive episode (MDE) recommend using either mood stabilizer monotherapy or the combination of a mood stabilizer with a selective serotonin reuptake inhibitor (SSRI). These guidelines are the result of **...**
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Treatment research in bipolar disorder: issues and recommendations
RJ Baldessarini - CNS drugs, 2002 - ingentaconnect.com
Abstract Bipolar (manic-depressive) disorder is one of the most common of the severe mental illnesses. Officially recognised forms comprise type I (with mania), type II (with hypomania), cyclothymia and a rapid-cycling subtype. International life- time prevalence estimates are 1 to 5% of **...**
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Do recent efficacy data on the drug treatment of acute bipolar depression support the position that drugs other than antidepressants are the treatment of choice?
HJ Möller, H Grunze… - European archives of psychiatry and …, 2006 - Springer
In some European countries, antidepressants have a long tradition of being the drugs of first choice in the treatment of acute bipolar depression. This tradition still has a strong impact on treatment decisions in rou- tine care (Kasper etal. 1999; Walden etal. 1999). How- ever, **...**
Cited by 31 - Related articles - BL Direct - All 3 versions

Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data
JR Calabrese, JD Guelfi… - Bipolar …, 2007 - Wiley Online Library
Results: Using intent-to-treat data, 81% of patients met criteria for marked improvement (>50% improvement from baseline in HAM-D score) at study endpoint. Patients were severely depressed at study entry (HAM-D of 25.2) and 47.6% responded as early as at one week of **...**
Cited by 32 - Related articles - BL Direct - All 5 versions

Acceleration and augmentation strategies for treating bipolar depression
LL Altshuler, MA Frye… - Biological psychiatry, 2003 - Elsevier
Combination strategies (also termed polypharmacotherapy) are commonly used in clinical practice to achieve maximum mood stabilization for bipolar illness (Nichol et al 1995; Solomon et al 1996; Freeman and Stoll 1998 and Frye et al 2000b). Factors associated with **...**
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[PDF] Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options
[PDF] from tranylcypromin.infoLN Yatham, JR Calabrese… - Bipolar disorders, 2003 - tranylcypromin.info
Bipolar Disorders 2003: S: 85-97 BIPOLAR DISORDERS ISSN 1398-5647 Review Article Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options Yatham LN, Calabrese JR, Kusumakar V. Bipolar depression: criteria for treatment **...**
Cited by 31 - Related articles - BL Direct - All 11 versions

Decision tree for the treatment of bipolar disorder
GS Sachs - 2003 - cat.inist.fr
Clinicians managing patients with bipolar disorder confront a myriad of complex treatment decisions. This complexity limits the practicality of treatment guidelines, which attempt to be comprehensive. A user-friendly guide can, however, be constructed by considering only **...**
Cited by 29 - Related articles - BL Direct - All 4 versions

Use of antidepressants to treat depression in bipolar disorder
[HTML] from psychiatryonline.orgRS El-Mallakh… - Psychiatric Services, 2002 - Am Psychiatric Assoc
For decades, clinicians and researchers did not distinguish between bipolar and unipolar depression. The safety and efficacy of antidepressants for the treatment of unipolar depression were studied, and the data were applied to the treatment of bipolar depression without **...**
Cited by 29 - Related articles - BL Direct - All 8 versions

Rates and predictors of developing a manic or hypomanic episode 1 to 2 years following a first hospitalization for major depression with psychotic features
MP DelBello, GA Carlson, M Tohen… - Journal of child and …, 2003 - liebertonline.com
Introduction: Although the presence of psychosis during major depression has been identi- fied as a predictor of later developing mania or hypomania, to our knowledge there have been no studies examining rates and predictors of developing a manic or hypomanic episode in **...**
Cited by 30 - Related articles - BL Direct - All 3 versions

Antidepressants and suicidal behavior in bipolar disorder
SL McElroy, R Kotwal, R Kaneria… - Bipolar disorders, 2006 - Wiley Online Library
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Cited by 29 - Related articles - BL Direct - All 5 versions

The current understanding of lamotrigine as a mood stabilizer
CG Hahn, L Gyulai, CF Baldassano… - The Journal of clinical …, 2004 - cat.inist.fr
Objective: To examine whether lamotrigine has a unique role in the treatment of bipolar disorder, we evaluated the results of recent clinical trials and molecular and cell biological studies on lamotrigine. Data Sources: Using keywords such as bipolar disorder, lamotrigine, **...**
Cited by 28 - Related articles - BL Direct - All 4 versions

Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks
[HTML] from nih.govSN Ghaemi, AP Wingo, MA Filkowski… - Acta psychiatrica …, 2008 - Wiley Online Library
Results: In seven trials (350 BPD patients) involving 12 contrasts, long-term treatments that included ADs yielded 27% lower risk of new depression vs. MS-only or no treatment [pooled relative risk, RR = 0.73; 95% CI 0.55–0.97; number-needed-to-treat (NNT) = 11], but 72% greater **...**
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Benefits and limitations of antidepressants and traditional mood stabilizers for treatment of bipolar depression
JF Goldberg… - Bipolar disorders, 2005 - Wiley Online Library
Results: The strengths and limitations of current studies are described and critically reviewed in order to present optimal strategies for effective pharmacotherapy. Clinical factors that can mitigate or confound simple bivariate relationships between antidepressant use and outcome **...**
Cited by 27 - Related articles - BL Direct - All 5 versions

Bipolar depression: relationship between episode length and antidepressant treatment
WG Frankle, RH Perlis… - Psychological …, 2002 - Cambridge Univ Press
WG FRANKLE," RH PERLIS, T. DECKERSBACH, LD GRANDIN, SM GRAY, GS SACHS ???
AA NIERENBERG From the Department of Psychiatry, Columbia University, New York, NY: and Partners Bipolar Treatment Center, Massachusetts General Hospital, Department of **...**
Cited by 26 - Related articles - BL Direct - All 4 versions

Why antidepressants are not antidepressants: STEP-BD, STAR* D, and the return of neurotic depression
N Ghaemi - Bipolar disorders, 2008 - Wiley Online Library
The widely held clinical view of 'antidepressants' as highly effective and specific for the treatment of all types of depressive disorders is exaggerated. This sobering conclusion is supported by recent findings from the NIMH-sponsored STEP-BD and STAR*D projects. **...**
Cited by 27 - Related articles - All 5 versions

Bipolar depression in a low-income primary care clinic
[HTML] from psychiatryonline.orgM Olfson, AK Das, MJ Gameroff… - American Journal of …, 2005 - Am Psychiatric Assoc
OBJECTIVE: This study estimated the proportion of patients attending an urban general medical practice with current major depression and a history of bipolar disorder and compared the history, presentation, and treatment of patients with unipolar and bipolar depression. **...**
Cited by 25 - Related articles - BL Direct - All 5 versions

Treatment emergent affective switch: a controlled study
RS Tamada, CK Issler, JA Amaral… - Bipolar …, 2004 - Wiley Online Library
Conclusion: TEAS was less severe, but had similar duration when compared with spontaneous mania. These results cannot directly answer the question of whether there is a causal relationship between antidepressant use and TEAS. While it is also possible that patients with longer **...**
Cited by 22 - Related articles - BL Direct - All 4 versions

The armamentarium of treatments for bipolar disorder: a review of the literature
DA Cousins… - The International Journal of …, 2007 - Cambridge Univ Press
Abstract To assess current pharmacotherapeutic options for bipolar disorder, with particular emphasis on the use of antipsychotic agents, Medline and EMBASE were searched between January 1980 and December 2005 using the keywords 'schizoaffective disorder' and 'bipolar disorder', **...**
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When Do Antidepressants Worsen the Course of Bipolar Disorder?
JF GOLDBERG - Journal of Psychiatric Practice, 2003 - journals.lww.com
Wolters Kluwer Health may email you for journal alerts and information, but is committed to maintaining your privacy and will not share your personal information without your express consent. For more information, please refer to our Privacy Policy. **...** Skip Navigation Links Home > May **...**
Cited by 19 - Related articles - BL Direct - All 2 versions

Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation
G Xia, P Gajwani, DJ Muzina… - The International …, 2008 - Cambridge Univ Press
Abstract This review focused on the treatment-emergent mania/hypomania (TEM) associated with repetitive transcranial magnetic stimulation (rTMS) treatment of depression. English-language literature published from 1966–2006 and indexed in Medline was searched. Ten of 53 **...**
Cited by 21 - Related articles - BL Direct - All 4 versions

Pharmacotherapy of bipolar depression: an update
ME Thase - Current psychiatry reports, 2006 - Springer
Bipolar affective disorder is a virulent illness with high rates of recurrence, disability, social impairment, and suicide. Although the manic or hypomanic episodes define the disorder, the depressions are more numerous and less responsive to treatment. As the initial depres- **...**
Cited by 18 - Related articles - BL Direct - All 5 versions

The role of lithium in the treatment of bipolar depression
Z Bhagwagar… - Clinical Neuroscience Research, 2002 - Elsevier
Bipolar depression is assuming increasing importance as perhaps the major challenge in the acute management of bipolar 1 disorder. Treatment guidelines suggest an overwhelming expert preference for the use of lithium as first line treatment rather than antidepressants. **...**
Cited by 17 - Related articles - All 3 versions

Paroxetine: safety and tolerability issues
DM Marks, MH Park, BJ Ham, C Han, AA Patkar… - 2008 - informahealthcare.com
Paroxetine is a selective serotonin re-uptake inhibitor (SSRI) available in immediate release and controlled release (CR) formulations. Paroxetine is the most potent inhibitor of serotonin re-uptake among the now available SSRIs. Paroxetine has been approved for the **...**
Cited by 16 - Related articles - All 4 versions

Treatment of bipolar depression: current status, continued challenges, and the STEP-BD approach
ME Thase, M Bhargava… - The Psychiatric clinics of North …, 2003 - cat.inist.fr
This article takes an evidence-based medicinal approach to the treatment of bipolar depression. Mood stabilizers are strongly recommended as the first line of treatment for milder bipolar depressive episodes, primarily because subsequent preventive therapy will be **...**
Cited by 16 - Related articles - BL Direct - All 3 versions

Antidepressant-associated switches from depression to mania in severe bipolar disorder
GA Carlson, SJ Finch, LJ Fochtmann… - Bipolar …, 2007 - Wiley Online Library
Results: The 76 respondents experienced 113 depressive episodes. Those prescribed ADs had more depressive episodes and spent more time depressed than non-users. A total of 23 depressive episodes in 17 respondents ended in a manic/hypomanic/mixed episode (20%). The time **...**
Cited by 15 - Related articles - BL Direct - All 6 versions

The management of individuals with bipolar disorder: a review of the evidence and its integration into clinical practice
[PDF] from gnmhealthcare.comGS Malhi, D Adams, CM Cahill, S Dodd… - Drugs, 2009 - ingentaconnect.com
Abstract. 2064 1. Aim, Method and Structure of Review 2065 1.1 Aim**...**
Cited by 15 - Related articles - All 6 versions

Bipolar depression: diagnostic and treatment considerations
ME THASE - Development and psychopathology, 2006 - Cambridge Univ Press
Abstract Bipolar affective disorder is a recurrent, disabling, and potentially lethal illness that typically begins early in life. Although the disorder is defined by the manic and hypomanic episodes, for most people the depression episodes are the more virulent aspect of the illness. **...**
Cited by 15 - Related articles - BL Direct - All 6 versions

Current drug use as risk factor for erectile dysfunction: results from an Italian epidemiological study
[PDF] from healthmegamall.comE Ricci, F Parazzini, V Mirone, C Imbimbo… - International journal of …, 2003 - nature.com
Several drugs have been associated with an increased risk of erectile dysfunction (ED). We analysed the role of pharmacological treatments on the risk of ED using data from a cross-sectional study on prevalence and risk factors for ED in the general population in Italy. A total of 2450 **...**
Cited by 14 - Related articles - BL Direct - All 8 versions

Clinical practice recommendations for bipolar disorder
[PDF] from monashdivision.com.auGS Malhi, D Adams, L Lampe… - Acta Psychiatrica …, 2009 - Wiley Online Library
Method: A comprehensive literature review of over 500 articles was undertaken using electronic database search engines (eg MEDLINE, PsychINFO and Cochrane reviews). In addition articles, book chapters and other literature known to the authors were reviewed. The **...**
Cited by 17 - Related articles - All 7 versions

Unmet needs in bipolar depression
MA Frye, MJ Gitlin… - Depression and anxiety, 2004 - Wiley Online Library
Bipolar disorders, particularly bipolar spectrum disorders, frequently go unrecognized and undiagnosed by clinicians and thus remain untreated or inappropriately treated. Although the symptoms of bipolar I disorder are widely acknowledged and recognized among clinicians, **...**
Cited by 14 - Related articles - BL Direct - All 5 versions

Current treatments for bipolar disorder: A review and update for psychologists.
RA Rivas-Vazquez, SL Johnson, GJ Rey… - Professional …, 2002 - psycnet.apa.org
Page 1. Current Treatments for Bipolar Disorder: A Review and Update for Psychologists Rafael A. Rivas-Vazquez Neurologic Center of South Florida and University of Miami School of Medicine Sheri L. Johnson University of Miami School of Psychology **...**
Cited by 14 - Related articles - BL Direct - All 5 versions

Bipolar disorder, antidepressants and induction of hypomania or mania. A systematic review
[PDF] from wfsbp.orgHM Visser… - World Journal of Biological …, 2005 - informahealthcare.com
Objective: The literature cautions against the induction of (hypo)mania owing to the use of antidepressants in bipolar disorder. Objectives of this review are to examine: (1) the evidence for this assumption; (2) underlying risk factors; and (3) the extent to which a mood stabilizer may **...**
Cited by 13 - Related articles - BL Direct - All 4 versions

Recent placebo-controlled acute trials in bipolar depression: focus on methodology
DJ Muzina… - The International Journal of …, 2003 - Cambridge Univ Press
Abstract The completion of three recent large-scale, double-blind controlled acute trials in bipolar I depression has improved our understanding of the management of major depressive episodes associated with bipolar disorder. In contrast to the cross-over designs used in the early **...**
Cited by 12 - Related articles - BL Direct - All 4 versions

[PDF] Impact of antidepressant continuation after acute positive or partial treatment response for bipolar depression: a blinded, randomized study
[PDF] from stanford.eduLL Altshuler, RM Post, G Hellemann… - J Clin …, 2009 - bipolarresearch.stanford.edu
Objective: To assess long-term outcome in bipolar disorder, subjects were prospectively followed after receiving acute treatment for bipolar depression. Method: Eighty-three outpatients with DSM-IV bipolar depression who were enrolled between March 1996 and November **...**
Cited by 13 - Related articles - All 4 versions

Long-term treatment of bipolar disorder with lamotrigine
JR Calabrese, MD Shelton, DJ Rapport… - Symposium Long-Term …, 2002 - cat.inist.fr
Bipolar depression is as debilitating as mania in bipolar disorder, but the treatment of bipolar depression has historically received less attention. To date, there is no mood stabilizer (liberally defined as a medication that decreases episode severity, duration, or frequency in one **...**
Cited by 37 - Related articles - BL Direct - All 3 versions

Adjunctive strategies in the treatment of refractory bipolar depression: clinician options in the absence of a systematic database
RM Post - Expert Opinion on Pharmacotherapy, 2005 - informahealthcare.com
Multiple approaches to enhancing antidepressant treatment response in bipolar depression are available and should, in many instances, be explored despite a lack of definitive controlled trial literature supporting their efficacy. Given that the morbidity of depression is three **...**
Cited by 11 - Related articles - BL Direct - All 3 versions

The" softer" end of the bipolar spectrum
R PIES - Journal of Psychiatric Practice, 2002 - journals.lww.com
Wolters Kluwer Health may email you for journal alerts and information, but is committed to maintaining your privacy and will not share your personal information without your express consent. For more information, please refer to our Privacy Policy. **...** PIES: Tufts University School of **...**
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[BOOK] Why am I still depressed?: recognizing and managing the ups and downs of bipolar II and soft bipolar disorder
JR Phelps… - 2006 - books.google.com
Why am I s till depressed^ ? Jim Phelps, MD foreword hy S. Nassir Ghaemi. MO. M.RH. Oireclor. Bipolar Di»ro>r Research Piofram, Dtpaitment of Psychiatry. Emory Unmully Recognizing and Managing the Ups and Downs of Bipolar II and Soft Bipolar Disorder ♦ Discover the **...**
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Bipolar depression: overview and commentary
RJ Baldessarini, E Vieta… - Harvard review of …, 2010 - informahealthcare.com
Depressive phases are the most prevalent component of bipolar disorders, even with modern treatment. Bipolar depressive morbidity is often misdiagnosed and is limited in response to available treatments. These conditions are especially debilitating and are associated with **...**
Cited by 13 - Related articles - All 4 versions

Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients
[PDF] from webnode.comRS El-Mallakh, SN Ghaemi, K Sagduyu… - Journal of affective …, 2008 - Elsevier
Prospective data from the first 1500 patients (62.7% with bipolar I, 30.1% with bipolar II, and 7.2% with NOS) treated in the STEP-BD database were examined and those who were euthymic for at least one month at study entry, subsequently developed a depressive episode, and **...**
Cited by 11 - Related articles - All 6 versions

Bipolar depression: a review of randomised clinical trials
PJ Goodnick - 2007 - informahealthcare.com
Randomised, controlled trials have been completed in the study of the response of bipolar depression to lithium, antiepileptic drugs, antidepressants (particularly the selective serotonin re-uptake inhibitors) and a few miscellaneous agents including pramipexole. In most cases, only **...**
Cited by 11 - Related articles - BL Direct - All 3 versions

Treatment options for bipolar depression
CL Bowden - Teleconference New Perspectives in Treating Bipolar …, 2005 - cat.inist.fr
Bipolar disorder is often misdiagnosed as major depressive disorder because of the high frequency of depressive symptomatology in many patients with bipolar disorder. Depressive episodes that are resistant to treatment may also be associated with a worse course of illness in bipolar **...**
Cited by 29 - Related articles - All 4 versions

[HTML] Chronic depression in bipolar disorder
[HTML] from psychiatryonline.orgRS El-Mallakh… - American Journal of Psychiatry, 2006 - Am Psychiatric Assoc
A 45-year-old woman with bipolar I disorder has been treated with various combinations of mood stabilizers and antidepressants for many years, but she continues to complain of chronic depressive symptoms. Numerous attempts to treat these symptoms, including changing her **...**
Cited by 10 - Related articles - BL Direct - All 6 versions

Mania associated with antidepressant treatment: comprehensive meta-analytic review
L Tondo, G Vázquez… - Acta Psychiatrica …, 2010 - Wiley Online Library
Results: The overall risk of mania with/without ADs averaged 12.5%/7.5%. The AD-associated mania was more frequent in BPD than MDD patients, but increased more in MDD cases. Tricyclic antidepressants were riskier than serotonin-reuptake inhibitors (SRIs); data for other **...**
Cited by 9 - Related articles - All 4 versions

[PDF] Evidence-based pharmacological treatment of geriatric bipolar disorder
[PDF] from uiowa.eduRC Young - Psychiatric Clinics of North America, 2005 - public-health.uiowa.edu
Elderly individuals who have bipolar (BP) disorder present a particular challenge to clinicians, health care services, and caregivers. They are a com- plex and heterogeneous group of patients who frequently have comorbid- ities and poor outcomes, including a high **...**
Cited by 9 - Related articles - View as HTML - All 4 versions

Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder
R Australian - 2009 - informahealthcare.com
Treatment recommendations: This guideline provides evidence-based recommendations for the management of bipolar disorder by phase of illness, that is acute mania, mixed episodes and bipolar depression, and the prophylaxis of such episodes. It specifies the roles of **...**
Cited by 9 - Related articles - All 4 versions

Lithium: updated human knowledge using an evidence-based approach: Part I: Clinical efficacy in bipolar disorder
EM Grandjean… - CNS drugs, 2009 - ingentaconnect.com
Abstract. 225 1. Efficacy in Acute Mania .226 1.1 Critical Assessment**...**
Cited by 11 - Related articles - All 5 versions

The broad clinical spectrum of bipolar disorder: implications for research and practice.
DJ Smith, SN Ghaemi… - Journal of …, 2008 - ncbi.nlm.nih.gov
The broad clinical spectrum of bipolar disorder: implications for research and practice. **...** Comment in: J Psychopharmacol. 2008 Jun;22(4):404-5; discussion 408. J Psychopharmacol. 2008 Jun;22(4):401; discussion 408. J Psychopharmacol. 2008 Jun;22(4):402-3; discussion **...**
Cited by 9 - Related articles - BL Direct - All 3 versions

[HTML] Antidepressants for bipolar depression
[HTML] from psychiatryonline.orgSN Ghaemi… - American Journal of Psychiatry, 2005 - Am Psychiatric Assoc
To the Editor: Meta-analysis represents an "observational study of studies." The benefits of random assignment and the removal of confounding bias within a sample are lost with meta-analysis, resulting in the problem of "heterogeneity" between study samples. Just as **...**
Cited by 8 - Related articles - All 3 versions

Bipolar II and the bipolar spectrum
P Skeppar… - Nordic journal of psychiatry, 2006 - informahealthcare.com
In studies made in the last decade, patients consulting doctors because of depression and anxiety have very often turned out to suffer from bipolar type II and similar conditions with alternating depression and hypomania/mania (the bipolar spectrum disorders - BP). Specifically, **...**
Cited by 8 - Related articles - BL Direct - All 6 versions

Antidepressants in bipolar depression
[PDF] from 217.219.179.27RS El–Mallakh, A Karippot… - Bipolar depression: a …, 2006 - books.google.com
ANTIDEPRESSANTS IN BIPOLAR DEPRESSION RifS. El–Mallakh, MD Anoop Karippot, MD S. Nassir Ghaemi, MD, MPH TREATMENT AND PREVENTION OF bipolar depression is a major prob- lem in the long-term treatment of bipolar illness. While about one-third of patients **...**
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Maintenance treatment in bipolar I disorder
RF Estevez… - Bipolar disorder: a clinician's guide to …, 2009 - books.google.com
108 Bipolar disorder: A clinician's guide to treatment management Refractory patients…
Cited by 8 - Related articles - All 2 versions

The changing landscape of psychopharmacology
JF Goldberg - Psychological treatment of bipolar disorder, 2004 - books.google.com
THERAPY AND TREATMENT ISSUES The Changing Landscape of Psychopharmacology CHAPTER SIX THE CHANGING LANDSCAPE OF PSYCHOPHARMACOLOGY JOSEPH F. GOLDBERG In the past decade, the pharmacotherapy of bipolar disorder has changed dramatically. **...**
Cited by 8 - Related articles

Treatment of bipolar depression
RM Post - Pharmacotherapy of Depression, 2011 - Springer
The challenge of treating depression in patients with bipolar illness has been both underestimated and understudied for a variety of reasons. The role of traditional unimodal antidepressants in bipolar illness had been highly controversial, and now with the publication of the results **...**
Cited by 8 - Related articles - All 4 versions

Clinical indicators for the use of antidepressants in the treatment of bipolar I depression
A Fagiolini, E Frank, CR Cherry, PR Houck... - Bipolar ..., 2002 - Wiley Online Library
Objectives: Current guidelines provide little practical information on the clinical characteristics of bipolar I patients who are likely to benefit from the combination of a mood stabilizer and an antidepressant. Rather, guidelines simply state that an adjunctive antidepressant is **...**
Cited by 8 - Related articles - BL Direct - All 3 versions

[PDF] An open trial of adjunctive escitalopram in bipolar depression
[PDF] from ohsu.eduM Fonseca, JC Soares, JP Hatch... - Journal of Clinical ..., 2006 - sakai.ohsu.edu
Received Feb. 1, 2005; accepted Dec. 1, 2005. From the Psychiatry Research Unit, Federal University of Rio Grande do Sul, Porto Alegre, Brazil (Drs. Fonseca and Kapczinski);
Cited by 9 - Related articles - BL Direct - All 5 versions

Treatment of bipolar depression.
SL Dubovsky - The Psychiatric clinics of North America, 2005 - ncbi.nlm.nih.gov
1. Psychiatr Clin North Am. 2005 Jun;28(2):349-70, vii. Treatment of bipolar depression. Dubovsky SL. Department of Psychiatry, State University of New York at Buffalo, 462 Grider Street, Buffalo, NY 14215, USA. Dubovsky@buffalo.edu. **...**
Cited by 8 - Related articles - All 3 versions

Chronic imipramine but not bupropion increases arachidonic acid signaling in rat brain: is this related to 'switching'in bipolar disorder&quest
[HTML] from nih.govHJ Lee, JS Rao, L Chang, SI Rapoport... - Molecular psychiatry, 2008 - nature.com
Agents effective against mania in bipolar disorder are reported to decrease turnover of arachidonic acid (AA) in phospholipids and expression of calcium-dependent AA-selective cytosolic phospholipase A 2 (cPLA 2) in rat brain. In contrast, fluoxetine, an antidepressant that is reported to **...**
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The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of ...
[PDF] from clinicum.atH Grunze, E Vieta, GM Goodwin... - World Journal of ..., 2010 - informahealthcare.com
Objectives. These guidelines are based on a first edition that was published in 2002, and have been edited and updated with the available scientific evidence until September 2009. Their purpose is to supply a systematic overview of all scientific evidence pertaining to the treatment of **...**
Cited by 9 - Related articles - All 11 versions

[PDF] Hippocrates and Prozac: the controversy about antidepressants in bipolar disorder
[PDF] from mbldownloads.comSN Ghaemi - Primary psychiatry, 2006 - mbldownloads.com
The controversy surrounding use of antidepressants in bipolar disorder **...** Overall, a scientifically sound assessment of the evidence regard- **...** Hippocratic approach to psychopharmacology, supports more caution **...** Needs Assessment:Clinicians **...**
Cited by 6 - Related articles - View as HTML - BL Direct - All 2 versions

Depressive subtypes and efficacy of antidepressive pharmacotherapy
[PDF] from globit.comJL Ayuso-Gutiérrez - World Journal of Biological Psychiatry, 2005 - informahealthcare.com
Efficacy studies suggest that all kinds of treatment have similar efficacy. For instance, according to a meta-analysis from 102 randomised controlled trials in major depression, there is no overall difference in efficacy between SSRIs and TCAs. Taking into consideration the **...**
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Medicating mood with maintenance in mind: bipolar depression pharmacotherapy
[PDF] from monashdivision.com.auGS Malhi, D Adams... - Bipolar disorders, 2009 - Wiley Online Library
Results: Partitioning treatment into acute and maintenance therapy is difficult based on the paucity of current evidence. The evidence from treatment trials favours the use of lithium and lamotrigine as first-line treatment in preference to valproate, and indicates that, for acute episodes, **...**
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Advancing the pharmacological treatment of bipolar depression
[HTML] from rcpsych.orgS Frangou - Advances in Psychiatric Treatment, 2005 - RCP
Bipolar disorder is a recurring, often chronic, illness characterised by periods of mania and depression with variable inter-episode recovery. For the majority of patients it is the depressive component of this illness that contributes to most of the associated morbidity, social disability and **...**
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An update on the treatment of bipolar depression
JM Azorin… - 2009 - informahealthcare.com
Background: Although depression accounts for a large part of the burden associated with bipolar disorder, its drug treatment has been under-studied. Objective: To provide the best available evidence supporting the pharmacotherapy of bipolar depression. Methods: A systematic **...**
Cited by 5 - Related articles - All 4 versions

Old drug, new data: REVISITING... LITHIUM THERAPY
[HTML] from rcpsych.orgIN Ferrier, LJ Ferrie… - Advances in Psychiatric Treatment, 2006 - RCP
) and Honorary Consultant Psychiatrist for Newcastle, North Tyneside and Northumberland Mental Health NHS Trust. He works in a clinical capacity for a regional service for patients with chronic affective disorders. His research interests are in psychopharmacology and the **...**
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Zonisamide for bipolar depression
MS Wilson… - 2007 - informahealthcare.com
In recent years, research into bipolar depression has increased. Each year, more studies are published using different agents to treat this condition. In addition to effectiveness and tolerability, bipolar depression research has sought agents that do not induce cycling or **...**
Cited by 6 - Related articles - BL Direct - All 3 versions

What drugs are best for bipolar depression?
CF Baldassano, SM Datto, L Littman… - Annals of clinical …, 2003 - Springer
Bipolar depression is a severe, potentially lethal disorder for which there are no specific, FDA- indicated pharmacotherapies. Research in this area has been limited, and most treatments are based on unsupported extrapolation from the treatment of unipolar depression, or **...**
Cited by 5 - Related articles - BL Direct - All 7 versions

[HTML] Antidepressant treatment-emergent affective switch in bipolar disorder: a prospective case-control study of outcome
[HTML] from scielo.brRS Tamada, JA Amaral, CK Issler… - Revista Brasileira de …, 2006 - SciELO Brasil
There is only one prospective and controlled study about cycle acceleration, published by Wehr et al. in 1988. 12 The authors followed 51 patients who were their own controls. In this study, half of the patients presented with rapid cycling and the investigators concluded that the **...**
Cited by 5 - Related articles - Cached - All 9 versions

[PDF] Evaluation and management of breakthrough depressive episodes
[PDF] from argos2001.orgPE Keck - JOURNAL OF CLINICAL PSYCHIATRY, 2004 - argos2001.org
Clinicians are faced with a diagnostic challenge when a bipolar patient reports breakthrough de- pressive symptomatology. Breakthrough depressive symptoms during treatment for a bipolar depres- sive episode may be a manifestation of recurrent bipolar depression or the **...**
Cited by 5 - Related articles - BL Direct - All 6 versions

Therapeutic armamentarium
RH Howland, ME Thase - 2002 - Wiley Online Library
Currently, a wide variety of therapies are available for the treat- ment of mood disorders. These therapies have been studied mainly in major depressive disorder and bipolar I disorder, although they also are commonly used in clinical practice for the treatment of such related mood **...**
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Treatment of acute depression in bipolar disorder
GS Sachs - Advances in treatment of bipolar disorder, 2005 - books.google.com
Chapter 3 Treatment of Acute Depression in Bipolar Disorder Gary S. Sachs, MD What treatment is best for the depressed phase of bipolar disor- der? This simple question can now be addressed with the help of far more pertinent study data than was available 5 years ago. Pre- viously, **...**
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The challenges of pharmacotherapy of bipolar depression
[PDF] from jatrosom.deME Thase… - Clinical Neuroscience Research, 2002 - Elsevier
Bipolar depression is disabling and its treatment represents a major challenge to clinicians. This article briefly reviews the major pharmacological treatment options. Use of mood stabilizers as the initial treatment for the type I form of bipolar depression is strongly recommended, **...**
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Antidepressants for bipolar depression
[PDF] from psychiatryonline.orgR HIRSCHFELD, LJ Fochtmann… - American Journal of …, 2005 - Am Psychiatric Assoc
Regarding antidepressant-induced mania, two studies comparing antidepressants without mood stabilizer to no treatment (placebo only) reported no mania in any patients: an oddity, if true, since it would suggest that even spontane- ous mania did not occur while those patients were **...**
Cited by 4 - Related articles - All 3 versions

[PDF] Rational antidepressant selection: applying evidence-based medicine to complex real-world patients
[PDF] from psycard.comM Zetin, CT Hoepner… - Psychopharmacology bulletin, 2006 - psycard.com
TABSTRACT ~ Every clinician faces the daily question of which antidepressant is best for a particular depressed patient. Double-blind studies submitted for US Federal Drug Administration marketing approval include only the “purest” population of patients, and the American Psychiatric **...**
Cited by 5 - Related articles - BL Direct - All 13 versions

Evidence-based pharmacotherapy of bipolar disorder
SN Ghaemi… - Evidence-based psychopharmacology, 2005 - books.google.com
Evidence-based pharmacotherapy of bipolar disorder S. Nassir Ghaemi and Douglas J. Hsu Cambridge Hospital and Harvard University, Boston, MA, USA Conventional wisdom regarding the prevalence of bipolar disorder in the general population is most commonly derived **...**
Cited by 4 - Related articles - All 2 versions

Adjunctive use of modafinil in bipolar patients: just another stimulant or not?
RC Shelton… - Current psychiatry reports, 2008 - Springer
Depression is much more common in the life course of people with bipolar disorder than mania or mixed states. Unfortunately, few established treatments are available, and new ones are needed. Modafinil is a novel stimulant approved for treating improving wake- fulness in **...**
Cited by 4 - Related articles - All 3 versions

A 25-year-old woman with bipolar disorder
GS Sachs - JAMA: the journal of the American Medical Association, 2001 - Am Med Assoc
DR PARKER: Ms G is a 25-year-old woman who is slowly coming to terms with her diagnosis of bipolar disorder. She lives with her boyfriend and currently attends school. She experienced 2 manic episodes resulting in inpatient psychiatry hospitalizations. Ms G has lost her **...**
Cited by 3 - Related articles - BL Direct - All 4 versions

[CITATION] Antidepressant-induced rapid cycling: another perspective
JA MatTes - Annals of Clinical Psychiatry, 2006 - Informa Healthcare
Cited by 3 - Related articles - BL Direct - All 3 versions

Managing bipolar disorders in children and adolescents
E Taylor - Nature Reviews Neurology, 2009 - nature.com
Bipolar disorders are recurrent disturbances in mood that include periods both of depression and mania. Classic bipolar disorders, with manic episodes lasting for at least several days, often start in adolescence, but are uncommon in earlier childhood. Treatment of mania in **...**
Cited by 8 - Related articles - All 3 versions

Treatment options for bipolar depression: a systematic review of randomized, controlled trials
E Vieta, J Locklear, O Günther… - Journal of clinical …, 2010 - journals.lww.com
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Cited by 4 - Related articles - All 5 versions

Pharmacologic treatment of geriatric mania
WM McDonald… - Current Psychiatry Reports, 2002 - Springer
Introduction The prevalence of mania in the geriatric population is diffi- cult to precisely determine. The most recent psychiatric epidemiologic survey, the National Comorbidity Study, did not include adults over the age of 65 years [1]. The Epidemiological Catchment **...**
Cited by 3 - Related articles - All 2 versions

The primacy of mania: a reconsideration of mood disorders
A Koukopoulos… - European Psychiatry, 2009 - Elsevier
In contemporary psychiatry, depression and mania are conceived as different entities. They may occur together, as in bipolar disorder, or they may occur separately, as in unipolar depression. This view is partly based on a narrow definition of mania and a rather broad **...**
Cited by 4 - Related articles - All 3 versions

Treatment advances in bipolar disorder—making up for lost time
PE Keck - Biological psychiatry, 2000 - journals.elsevierhealth.com
Biological Psychiatry, Volume 48, Issue 6, Pages 430-432,
15 September 2000, Authors:Paul E Keck.
Cited by 3 - Related articles - Cached - All 9 versions

[PDF] Exercise and mood: exploring the role of exercise in regulating stress reactivity in bipolar disorder
[PDF] from umaine.eduTM Edenfield - 2007 - library.umaine.edu
Page 1. EXERCISE AND MOOD: EXPLORING THE ROLE OF EXERCISE IN REGULATING STRESS REACTIVITY IN BIPOLAR DISORDER By Teresa M. Edenfield BS Florida State University, 2001 MA University of Maine, 2004 A THESIS Submitted in Partial Fulfillment of the **...**
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Pharmacotherapy for Bipolar Depression: A Review of the Evidence
TF Aarre… - Current Psychiatry Reviews, 2008 - ingentaconnect.com
Nordfjord Psychiatric Centre, Nordfjordeid, Norway; Department of Clinical Cancer Research, The Norwegian Radium hospital, Rikshospitalet University Hospital, Oslo, Norway, and Faculty Division the Norwegian Radium Hospital, Uni- versity of Oslo, Oslo, **...**
Cited by 3 - Related articles - All 2 versions

[BOOK] **Bipolar depression: a comprehensive guide**
RS El-Mallakh… - 2006 - books.google.com
Note: The authors have worked to ensure that all information in this book is accurate at the time of publication and consistent with general psychiatric and medical standards, and that information concerning drug dosages, schedules, and routes of administration is accurate at the time **...**
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[HTML] **双相情感障碍临床治疗进展**
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单相抑郁障碍通常指单相抑郁或重性抑郁障碍（MDD）。单相躁狂或单纯躁狂（pure mania）**因相**对少见，故 DSM **和** ICD **未将**单相躁狂单独分类，而是把所有的躁狂和轻躁狂，即使无抑郁发作都视为双相。**我国学者**对此持保留态度，单相躁狂虽少，但确实存在，不应归入双相情感障碍。 **...**
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[PDF] **双相情感障碍联合治疗研究进展与临床评价**
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Page 1. **双相情感障碍**联合治疗研究进展与临床评价 **蒋**锋，汤宜朗，王传跃（**首都医科大学附属北京安定医院，北京市**１０００８８） **中**图分类号８９７１ ＊． ４ **文献**标识码Ａ **文章**编号１６７２ －２１２４（２００３）０５－。２７１－。 **摘要目的**：**研究双相情感障碍**联合治疗的进展 **...**
Cited by 4 - Related articles - All 6 versions

Clinical psychopharmacology and other somatic therapies
PJ Perry, HJ Wehring, B Alexander… - The medical basis of …, 2008 - Springer
Abstract The somatic treatment chapter consists of five narrative sections that include the pharmacotherapeutic agents indicated in the treatment of schizophrenia, depression, mania, all five anxiety disorders, and dementia. An additional section summarizes the hypnotic agents currently **...**
Cited by 2 - Related articles

Pharmacological management of bipolar depression
P Haddad… - Acta Psychiatrica Scandinavica, 2002 - Wiley Online Library
Among psychiatric illnesses bipolar disorder (BPD) ranks second only to unipolar depression as a cause of global disability (1). Hospitalized patients spend approximately 20% of their lifetime from the onset of their disorder in episodes (2). Fifteen per cent of sufferers commit **...**
Cited by 2 - Related articles - BL Direct - All 6 versions

Is monotherapy as good as polypharmacy in long-term treatment of bipolar disorder?
M Alda… - … journal of psychiatry. Revue canadienne de …, 2009 - ncbi.nlm.nih.gov
1. Can J Psychiatry. 2009 Nov;54(11):719-25. Is monotherapy as good as polypharmacy in long-term treatment of bipolar disorder? Alda M, Yatham LN. Department of Psychiatry, Dalhousie University, Halifax, Nova Scotia. malda@dal.ca. **...**
Cited by 2 - Related articles - All 3 versions

Mood stabilizers
DJ Muzina, DE Kemp… - 2008 - Wiley Online Library
Introduction A highly recurrent and often chronic affective illness such as bipolar disorder produces significant distress and dys- function, even when correctly diagnosed and treated. The unique clinical challenges posed by this chronic illness include various acute phases of mood **...**
Cited by 2 - Related articles - All 2 versions

[HTML] **The return of fixed combinations in psychiatry: fluoxetine and olanzapine combination**
[HTML] from nih.govRC Shelton - Therapeutics and Clinical Risk Management, 2006 - ncbi.nlm.nih.gov
Fixed combination psychotropics, such as a combination of a tricyclic and a typical antipsychotic, were widely prescribed a generation ago. These products were plagued by a number of problems, including serious side effects, which caused them to fall out of favor. More **...**
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[HTML] **The neurobiology of the switch process in bipolar disorder: a review**
[HTML] from nih.govG Salvadore, JA Quiroz… - The Journal of clinical …, 2010 - ncbi.nlm.nih.gov
The singular phenomenon of switching from depression to its opposite state of mania or hypomania, and vice versa, distinguishes bipolar disorder (BPD) from all other psychiatric disorders. Despite the fact that it is a core aspect of the clinical presentation of BPD, the **...**
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Bipolar disorder in children and adolescents
E Leibenluft, DP Dickstein - Wiley Online Library
There has been a recent marked upsurge in interest in pediatric bipolar disorder (PBD), with almost twice as many articles published on the subject in the past 5 years as in the entire previous decade. Several factors may be contributing to this trend. First, while it is clear that **...**
Cited by 2 - Related articles

[HTML] **Approaching the challenge of bipolar depression: results from STEP-BD**
[HTML] from psychiatryonline.orgSM Strakowski - American Journal of Psychiatry, 2007 - Am Psychiatric Assoc
Although the diagnosis of bipolar disorder is defined by the occurrence of mania or hypomania, in fact, depressive episodes and symptoms tend to dominate the course of the illness (1). However, treatments for bipolar depression are much less well defined than those for **...**
Cited by 2 - Related articles - BL Direct - All 5 versions

Treatment of bipolar depression: focus on pharmacologic therapies
PB Mitchell… - Expert Review of Neurotherapeutics, 2005 - ingentaconnect.com
10.1586/14737175.5.1.69 © 2005 Future Drugs Ltd. ISSN 1473-7175 69 **...** CONTENTS Disability Overview of the treatment of bipolar disorder Aims & methods Evidence: short-term acute treatment of bipolar depression Evidence: long-term prophylactic treatment of bipolar depression **...**
Cited by 2 - Related articles - BL Direct - All 3 versions

The treatment of depression
AS Hale - 2005 - Wiley Online Library
The treatment of depression has changed fundamentally in recent years. In many countries, the first-line treatment of depression utilizes talking therapies, with anti- depressant medication offered as a second-line treatment.This has been understood as in part reflecting a generally **...**
Cited by 2 - Related articles - All 3 versions

[HTML] Manic episodes during antidepressant treatment in bipolar disorder
[HTML] from scielo.brRS Tamada… - Revista Brasileira de Psiquiatria, 2003 - SciELO Brasil
Descritores: Depressão bipolar. Antidepressivo. Tratamento. Efeitos adversos. Iatrogenia. **...** OBJECTIVES: To review the literature on antidepressant-induced mania, its incidence, clinical presentation, risk factors and treatment. METHODS: A Medline search of studies **...**
Cited by 3 - Related articles - Cached - All 2 versions

双相情感障碍抑郁发作的治疗进展
刘海静… - **山**东精神医学, 2006 - cqvip.com
首页; **期刊大全**; **知**识社区; **学者空**间; **学**术机构; 专题导读; **会**议展览; **教育培**训; **登**录 **注册 充**值中心 **客服中心**. 维普资讯 **中文期刊**·专业文章. 维普专业检索. >> **摘要**. **双相情感障碍抑郁**发作的治疗进展. 评论推荐. **在**线阅读 **下**载全文收藏本文. **刘海静**[1] **何新芳**[2]. **...**
Cited by 3 - Related articles - All 5 versions

[PDF] Inducao de mania durante o tratamento com antidepressivos no transtorno bipolar^*
[PDF] from scielo.brRS Tamada… - REVISTA BRASILEIRA DE PSIQUIATRIA, 2003 - SciELO Brasil
Introdução Nos últimos anos houve significativo aumento do número de estudos publicados sobre o tratamento do Transtorno Bipo- lar. A maior parte destes diz respeito às fases de mania e profi- laxia, sendo que o tratamento dos episódios depressivos tem recebido menor **...**
Cited by 4 - Related articles - View as HTML - BL Direct - All 4 versions

On being bipolar without being bipolar
JF Goldberg - Journal of Psychopharmacology, 2008 - jop.sagepub.com
The paper in this issue by Smith and colleagues raises provoc- ative and important issues of both theoretical and clinical rele- vance to the basic nosology of affective disorders. One element of their treatise involves controversies about defining the ele- ments, which comprise the **...**
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Duloxetine-induced hypomania: case report and brief review of the literature on SNRIs-induced mood switching
V Peritogiannis, K Antoniou, V Mouka… - Journal of …, 2009 - jop.sagepub.com
Manic switching during antidepressant treatment has been reported with every class of antidepressant drugs. Serotonin-noradrenaline reuptake inhibitors (SNRIs) have been increasingly used for the treatment of unipolar and bipolar depression and are well tolerated and sufficiently **...**
Cited by 2 - Related articles - All 4 versions

[HTML] Emerging Treatment Strategies for Bipolar Disease
[HTML] from medscape.orgML Korn… - 2002 - medscape.org
Emil Kraepelin [1] characterized manic-depressive illness as a series of discrete affective episodes interspersed with periods of full recovery. He contrasted this course with the progressive and unremitting one of schizophrenia. However, many patients with manic-depressive **...**
Cited by 1 - Related articles - Cached - All 2 versions

Treatment Goals of Bipolar Disorder
J Goldberg, I Kuo… - Medscape Psychiatry & Mental …, 2003 - medscape.org
Bipolar affective disorder is reported to have a prevalence of approximately 1% to 2% of the population; in its more heterogeneous forms, this estimate may be closer to 4%. [1] The illness involves high morbidity as well as mortality and is ranked by the World Health **...**
Cited by 1 - Related articles - Cached - All 3 versions

[PDF] Anxiety and bipolar disorder
[PDF] from aplus.netSN Ghaemi - Medscape Family Medicine/Primary Care, 2004 - kimbarrus.site.aplus.net
Anxiety and mood go together. Most patients treated by mental health professionals are the worried well; they experience some combination of depression and anxiety, which used to be called "neurotic depression," a label later divided among a number of different categories: major **...**
Cited by 1 - Related articles - View as HTML - All 7 versions

[HTML] Progress in the Treatment of Bipolar Depression: Advances and Challenges
[HTML] from psychiatrictimes.comDE Kemp, K Gao, DJ Muzina… - Psychiatric Times, 2006 - psychiatrictimes.com
In the lamotrigine study, the rate of withdrawals due to adverse events was similar with active drug and placebo. In the olanzapine trial, patients receiving olanzapine monotherapy were most likely to discontinue treatment because of excessive somnolence, and had higher dropout **...**
Cited by 1 - Related articles - Cached - All 6 versions

[BOOK] Suicide in bipolar depression
[PDF] from 217.219.179.27MJ Ostacher… - 2006 - books.google.com
SUICIDE IN BIPOLAR DEPRESSION Michael J. Ostacher, MD, MPH Polina Eidelman, BA
Dearest, I feel certain I am going mad again. I feel we can't go through another of those terrible times. And I shan't recover this time. I begin to hear voices, and I can't concentrate. So I **...**
Cited by 1 - Related articles - All 4 versions

[BOOK] Managing bipolar disorder: A cognitive behavior treatment program therapist guide
M Otto, N Reilly-Harrington, JN Kogan, A Henin… - 2008 - books.google.com
1 Oxford University Press, Inc., publishes works that further Oxford University's objective of excellence in research, scholarship, and education. Oxford New York Auckland Cape Town Dar es Salaam Hong Kong Karachi Kuala Lumpur Madrid Melbourne Mexico City Nairobi New Delhi **...**
Cited by 1 - Related articles

[HTML] Pharmaceutical treatment of acute bipolar depression
[HTML] from nih.govKN Fountoulakis - F1000 medicine reports, 2010 - ncbi.nlm.nih.gov
The treatment of bipolar depression is one of the most challenging fields in contemporary psychiatry. The best data concern the antipsychotics quetiapine and the olanzapine-fluoxetine combination. However, the usefulness of antidepressants in bipolar depression remains **...**
Cited by 1 - Related articles - All 4 versions

[PDF] Irritability in pediatric mania
[PDF] from fioriti.itBA Rich… - Clinical Neuropsychiatry, 2006 - fioriti.it
Although the study of pediatric bipolar disorder (BPD) and childhood mania is of increasing interest, clinical criteria for diagnosing the illness in children continue to be debated. The role of irritability is central to this controversy. Of particular importance is whether irritable **...**
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[PDF] Bipolar depression
[PDF] from currentpsychiatry.comSN Ghaemi… - 2006 - currentpsychiatry.com
• add an antidepressant if the maximum benefit of the mood stabilizer has already been achieved
• or add a second mood stabilizer if the patient has a his- tory of poor response to antidepressants
or if the anti- depressant options are not promising. Most data supporting these **...**
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Diagnostic and Clinical Management Approaches to Bipolar Depression, Bipolar II and Their Comorbidities
G Perugi, SN Ghaemi… - 2006 - Wiley Online Library
The correct diagnosis of bipolar depression has major implications for clinical practice. It has emerged as a major challenge in the treatment of bipolar disorder. Hence the need for a chapter to focus on it. During the last two decades, neuropsychopharmacology has developed **...**
Cited by 1 - Related articles - All 2 versions

[PDF] Bipolar Disorder—A Focus on Depression
[PDF] from buffalo.eduMA Frye - N Engl J Med, 2011 - smbs.buffalo.edu
This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.
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Efficacy and safety of two treatment algorithms in bipolar depression consisting of a combination of lithium, lamotrigine or placebo and paroxetine
MLM Van Der Loos, P Mulder… - Acta Psychiatrica …, 2010 - Wiley Online Library
Objective: In a previous paper, we reported about the efficacy of the addition of lamotrigine to lithium in patients with bipolar depression. In the second phase of this study paroxetine was added to ongoing treatment in non-responders. **...** Method: Bipolar depressed patients (n = 124) **...**
Cited by 2 - Related articles - All 4 versions

[HTML] Managing bipolar depression
[HTML] from nih.govR Pary, PR Matuschka, S Lewis… - Psychiatry (Edgmont), 2006 - ncbi.nlm.nih.gov
What should the clinician do when confronted with a patient who has depressive symptoms? Seek the proper diagnosis. Question the patient about depressive symptoms over a two-week course that interferes with social and/or occupational functioning. Determine if there is **...**
Cited by 1 - Related articles - All 2 versions

PDF] Neurobiologia do transtorno de humor bipolar e tomada de decisão na abordagem psicofarmacológica
[PDF] from scielo.brR Machado-Vieira, AW Schwartzhaupt… - Rev. Psiquiatr. Rio …, 2003 - SciELO Brasil
O Transtorno do Humor Bipolar (THB) ca- racteriza-se por oscilações do humor que cau- sam prejuízos significativos no âmbito biopsi- cossocial, com critérios específicos para seus subdiagnósticos (DSM-IV). O surgimento de novos fármacos com propriedade de estabilizar o humor, o **...**
Cited by 1 - Related articles - View as HTML - All 6 versions

[CITATION] Bipolar depression
RMA Hirschfeld… - MEDICAL PSYCHIATRY, 2005 - MARCEL DEKKER
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[HTML] **Building Foundations Toward Recovery in Bipolar Disorder**
[HTML] from medscape.orgML Korn - medscape.org
Although bipolar disorder was originally seen as a disorder of episodic affective relapses alternating with periods of remission, it has become increasingly clear that this is not the rule. Most individuals with the disorder suffer from chronic symptoms that result in ongoing psychological and **...**
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Evidence-Based Treatment of Bipolar Disorder: An Update
R Perlis - medscape.org
Even though there has been a recent proliferation of randomized controlled trial (RCT) data in the treatment of bipolar disorder, as well as the publication of 2 new US treatment guidelines over the past year -- the updated Texas Implementation of Medication Algorithms (TIMA) **...**
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[HTML] **Easing the Burden of Bipolar Disorder: From Urgent Situations to Remission**
[HTML] from nih.govAB Depression - ncbi.nlm.nih.gov
Bipolar disorder is associated with increased lost days from work, 1 reduced vocational and residential status, 2 and increased psychosocial impairment. 3 People with bipolar disorders are symptomatic about half of the time, and depressive symptoms occur much more frequently than **...**
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2 Bipolar Disorder
TCDME Thase - 2010 - Springer
Abstract: Bipolar Disorder has long been considered to be a condition best managed by py- chopharmacologically and psychotherapy specific to bipolar disorder has only recently been a subject of interest. In our overview in this chapter on bipolar disorder we examine nosology of the DSM-IV **...**
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[PDF] **Antidepressants for bipolar depression: Tips to stay out of trouble**
[PDF] from currentpsychiatry.comLS Altman - currentpsychiatry.com
When it makes sense to use them and for how long **...** 22 VOL. 4, NO. 7 / JULY 2005 Current p SYCHIATRY **...** MAINTENANCE THERAPY Antidepressants may have modest efficacy in acute bipolar depression, but they have not shown benefit—with or without mood stabilizers—in **...**
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Lithium: Still a Major Option in the Management of Bipolar Disorder
RW Licht - CNS Neuroscience & Therapeutics - Wiley Online Library
Correspondence Rasmus W. Licht, MD, Ph.D., Mood Disorders Research Unit, Aarhus University Hospital, Risskov, Skovagervej 2, 8240 Risskov, Denmark. Tel.: +45 77893851; Fax: +45 77893859; E-mail: rasmus.lichtl@ps.rm.dk **...** Still after more than 50 years, lithium is a **...**

Differential diagnosis of bipolar disorder.
JF Goldberg - Primary Psychiatry, 2010 - medscape.org
The following test-and-teach case is an educational activity modeled on the interactive grand rounds approach. The questions within the activity are designed to test your current knowledge. After each question, you will be able to see whether you answered correctly **...**
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[HTML] **Focus Points**
[HTML] from primarypsychiatry.comB Zimmer - Primary Psychiatry, 2004 - primarypsychiatry.com
• While antiepileptic drugs (AEDs) have been used clinically and successfully in the treatment of bipolar affective disorders, only three AEDs have placebo-controlled studies to provide evidence-based support for their usage. **...** • Lamotrigine is the only AED shown with **...**
Cached

[HTML] **Faculty Affiliation and Disclosure**
[HTML] from cnsspectrums.comKN Fountoulakis - CNS Spectr, 2008 - cnsspectrums.com
CNS Spectrums: Bridging the clinical information needs of psychiatrists and neurologists. Featuring content on: addictive disorders, anxiety disorders, ADHD, autism, bipolar, eating disorders, neurological disorders.
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Bipolar depression: Diagnosis and treatment
DJ Muzina, DE Kemp, LN Yatham… - Bipolar disorder: a …, 2009 - books.google.com
20 Bipolar disorder: A clinician's guide to treatment management What other somatic therapies should be considered for refractory bipolar depression?..... 33 Clinical recommendations..... 34 References..... **...**
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Acute Bipolar Depression
PW Wang… - How to practice evidence-based …, 2010 - books.google.com
23 Acute Bipolar Depression Po W. Wang, MD Terence A. Ketter, MD Setting The patient was seen in an academic outpatient practice setting. The surrounding population is of high educational attainment and upper socio- economic status and ethnically diverse. The patient **...**
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[CITATION] Diagnosis and Treatment of Depression (MDD) and Bipolar Disorder (BPD) in Children and Adolescents
DP Dickstein, DS Pine… - The Physician's Guide …, 2006 - McGraw-Hill Professional
Related articles - All 2 versions

The Texas Implementation of Medication Algorithms on the Use of Anticonvulsants in Bipolar I Disorder
T Suppes… - medscape.com
It is only within the last 15 years that companies have begun to focus on the use of anticonvulsants in the treatment of bipolar disorder, and many new drugs have entered the market during that time. Although anticonvulsants have shown efficacy in the treatment of bipolar I disorder (**...**
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Class effect of pharmacotherapy in bipolar disorder: fact or misbelief?
[HTML] from annals-general-psychiatry.comKN Fountoulakis, X Gonda… - Annals of …, 2011 - annals-general-psychiatry.com

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[CITATION] Olanzapine/fluoxetine combination: Evidence for using the first treatment indicated for bipolar depression
RC Shelton
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Antidepressants and Bipolar I Affective Disorder
ME Thase - medscape.com
Despite the magnitude of this problem, only 1 treatment -- the proprietary combination of olanzapine and fluoxetine -- has ever received the US Food and Drug Administration's (FDA) approval for the specific indication of bipolar depression. Moreover, whereas antidepressants are **...**
Related articles - All 2 versions

[CITATION] Clinical News & Knowledge: Dissociative Disorders
JT Nigg - Psychiatric Times, 2009
Related articles - All 4 versions

Pharmacological treatment of bipolar depression
AH Young… - 2009 - Wiley Online Library
Bipolar disorders are characterized by episodes of mania/ hypomania and depression and are estimated in the pop- ulation to have a lifetime prevalence of approximately 2% [1,2]. The impact of bipolar disorders has recently been estimated to amount to 2% of all disability-adjusted **...**
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Reply to Dr Baldessarini's Comments on
TK Birkenhäger, WW van den Broek… - Journal of Clinical …, 2008 - journals.lww.com
We agree that the superior efficacy of imipramine in psychotic depression could be influenced by the greater level of severity in our particular sample. Indeed, we did perform a second regression analysis (presented in the Results section of our article)-which included baseline **...**
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The Role of Antidepressants in Bipolar Disorder
BI Yerevanian - Bipolar Psychopharmacotherapy - Wiley Online Library
The clinical use of antidepressants in bipolar disorder is a subject of controversy. The clinician treating bipolar disorder is often faced with compelling reasons to consider the use of antidepressants in bipolar depression as well as during the maintenance phase. In fact, antidepressants **...**

[HTML] Bipolar Depression Defined
[HTML] from primarypsychiatry.comGJ Kennedy - Primary Psychiatry, 2008 - primarypsychiatry.com
Treatment of bipolar depression is both a challenge and a paradox. It is a challenge because persistent disability and recurrence are common, and a paradox because antidepressants appear to be counterproductive. Although bipolar depression in late life is not common, the **...**
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R Depression
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Treating bipolar depression–antidepressants and alternatives: a critical review of the literature
A Tundo, P Cavalieri, S Navari… - Acta Neuropsychiatrica - Wiley Online Library
Acta Neuropsychiatrica 2011 All rights reserved DOI: 10.1111/j.1601-5215.2011.00542.x **...**
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S, Marchetti F. Treating bipolar depression – antidepressants and alternatives: a critical **...**
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260 Bipolar disorder: A clinician's guide to treatment management 1968–1979 (DSM-II).
273 Prospective trials 273 Discontinuation trials.Chapter ten: Lithium in the **...**
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A survey of antidepressant prescribing practices in major depression with comorbid attention-deficit hyperactivity disorder
GI Papakostas, TJ Petersen, RH Perlis… - Journal of clinical …, 2006 - journals.lww.com
Little is known with regard to which factors influence the antidepressant prescribing practices
of clinicians when treating patients with major depressive episodes. Regarding the treatment
of major depressive disorder (MDD), existing guidelines such as those of the American **...**
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Transition to Mania During Treatment of Bipolar Depression
RH Perlis, MJ Ostacher, JF Goldberg… - …, 2010 - nature.com
Some individuals with bipolar disorder transition directly from major depressive episodes to
manic, hypomanic, or mixed states during treatment, even in the absence of antidepressant
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Литература 1. American Psychiatric Association: Practice Guideline for the Treatment of Patients
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H Grunze… - Handbuch der Psychopharmakotherapie, 2008 - Springer
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Sr. Editor: Agradezco los comentarios de Vieta et al, aunque me gustaría matizar algunos aspectos mencionados por estos autores. En primer lugar, aunque es cierto que los pacientes con historia de depresión y un episodio hipomaníaco deben ser diagnosticados de trastorno bipolar **...**

[HTML] Bipolar Bozukluk-Manik Depresif
[HTML] from google.comKE NEDİR - sites.google.com
Duygu durumu fazla oynak, kah göklerde gezen kah yerin yedi kat dibine batan kişilere “manik depresif” dendiğini zaman zaman duyarız. Aslında hayatında en az bir “mani” atağı geçirmiş insanlara bu teşhisi koyarız. **...** Mani, kişinin kendisini olağanüstü iyi hissettiği bir hastalık **...**
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Record 1 of 183

Author(s): Sachs, GS (Sachs, Gary S.); Dupuy, JM (Dupuy, Jamie M.); Wittmann, CW (Wittmann, Curtis W.)

Title: The Pharmacologic Treatment of Bipolar Disorder

Source: JOURNAL OF CLINICAL PSYCHIATRY, 72 (5): 704-715 MAY 2011

ISSN: 0160-6689

DOI: 10.4088/JCP.10m06523

Record 2 of 183

Author(s): Tundo, A (Tundo, Antonio); Cavalieri, P (Cavalieri, Paola); Navari, S (Navari, Serena); Marchetti, F (Marchetti, Fulvia)

Title: Treating bipolar depression - antidepressants and alternatives: a critical review of the literature

Source: ACTA NEUROPSYCHIATRICA, 23 (3): 94-105 JUN 2011

ISSN: 0924-2708

DOI: 10.1111/j.1601-5215.2011.00542.x

Record 3 of 183

Author(s): Chen, J (Chen, Jun); Fang, YR (Fang, Yiru); Kemp, DE (Kemp, David E.); Calabrese, JR (Calabrese, Joseph R.); Gao, KM (Gao, Keming)

Title: Switching to Hypomania and Mania: Differential Neurochemical, Neuropsychological, and Pharmacologic Triggers and Their Mechanisms

Source: CURRENT PSYCHIATRY REPORTS, 12 (6): 512-521 DEC 2010

ISSN: 1523-3812

DOI: 10.1007/s11920-010-0157-z

Record 4 of 183

Author(s): Sidor, MM (Sidor, Michelle M.); MacQueen, GM (MacQueen, Glenda M.)

Title: Antidepressants for the Acute Treatment of Bipolar Depression: A Systematic Review and Meta-Analysis

Source: JOURNAL OF CLINICAL PSYCHIATRY, 72 (2): 156-167 FEB 2011

ISSN: 0160-6689

DOI: 10.4088/JCP.09r05385gre

Record 5 of 183

Author(s): Brooks, JO (Brooks, John O., III); Goldberg, JF (Goldberg, Joseph F.); Ketter, TA (Ketter, Terence A.); Miklowitz, DJ (Miklowitz, David J.); Calabrese, JR (Calabrese, Joseph R.); Bowden, CL (Bowden, Charles L.); Thase, ME (Thase, Michael E.)

Title: Safety and Tolerability Associated With Second-Generation Antipsychotic Polytherapy in Bipolar Disorder: Findings From the Systematic Treatment Enhancement Program for Bipolar Disorder

Source: JOURNAL OF CLINICAL PSYCHIATRY, 72 (2): 240-247 FEB 2011

ISSN: 0160-6689

DOI: 10.4088/JCP.09m05214yel

Record 6 of 183

Author(s): Nivoli, AMA (Nivoli, Alessandra M. A.); Colom, F (Colom, Francesc); Murru, A (Murru, Andrea); Pacchiarotti, I (Pacchiarotti, Isabella); Castro-Loli, P (Castro-Loli, Piero); Gonzalez-Pinto, A (Gonzalez-Pinto, Ana); Fountoulakis, KN (Fountoulakis, Kostas N.); Vieta, E (Vieta, Eduard)

Title: New treatment guidelines for acute bipolar depression: A systematic review

Source: JOURNAL OF AFFECTIVE DISORDERS, 129 (1-3): 14-26 MAR 2011

ISSN: 0165-0327
DOI: 10.1016/j.jad.2010.05.018

Record 7 of 183

Author(s): Rakofsky, JJ (Rakofsky, Jeffrey J.); Dunlop, BW (Dunlop, Boadie W.)

Title: Treating Nonspecific Anxiety and Anxiety Disorders in Patients With Bipolar Disorder: A Review

Source: JOURNAL OF CLINICAL PSYCHIATRY, 72 (1): 81-90 JAN 2011
ISSN: 0160-6689
DOI: 10.4088/JCP.09r05815gre

Record 8 of 183

Author(s): El-Mallakh, RS (El-Mallakh, Rif S.); Elmaadawi, AZ (Elmaadawi, Ahmed Z.); Loganathan, M (Loganathan, Muruga); Lohano, K (Lohano, Kavita); Gao, YL (Gao, Yonglin)

Title: Bipolar Disorder: An Update

Source: POSTGRADUATE MEDICINE, 122 (4): 24-31 JUL 2010
ISSN: 0032-5481

Record 9 of 183

Author(s): Frye, MA (Frye, Mark A.)

Title: Bipolar Disorder - A Focus on Depression

Source: NEW ENGLAND JOURNAL OF MEDICINE, 364 (1): 51-59 JAN 6 2011
ISSN: 0028-4793

Record 10 of 183

Author(s): Salvadore, G (Salvadore, Giacomo); Quiroz, JA (Quiroz, Jorge A.); Machado-Vieira, R (Machado-Vieira, Rodrigo); Henter, ID (Henter, Ioline D.); Manji, HK (Manji, Husseini K.); Zarate, CA (Zarate, Carlos A., Jr.)

Title: The Neurobiology of the Switch Process in Bipolar Disorder: A Review

Source: JOURNAL OF CLINICAL PSYCHIATRY, 71 (11): 1488-1501 NOV 2010
ISSN: 0160-6689
DOI: 10.4088/JCP.09r05259gre

Record 11 of 183

Author(s): Correa, R (Correa, R.); Akiskal, H (Akiskal, H.); Gilmer, W (Gilmer, W.); Nierenberg, AA (Nierenberg, A. A.); Trivedi, M (Trivedi, M.); Zisook, S (Zisook, S.)

Title: Is unrecognized bipolar disorder a frequent contributor to apparent treatment resistant depression?

Source: JOURNAL OF AFFECTIVE DISORDERS, 127 (1-3): 10-18 DEC 2010
ISSN: 0165-0327
DOI: 10.1016/j.jad.2010.06.036

Record 12 of 183

Author(s): Perlis, RH (Perlis, Roy H.); Ostacher, MJ (Ostacher, Michael J.); Goldberg, JF (Goldberg, Joseph F.); Miklowitz, DJ (Miklowitz, David J.); Friedman, E (Friedman, Edward); Calabrese, J (Calabrese, Joseph); Thase, ME (Thase, Michael E.); Sachs, GS (Sachs, Gary S.)

Title: Transition to Mania During Treatment of Bipolar Depression

Source: NEUROPSYCHOPHARMACOLOGY, 35 (13): 2545-2552 DEC 2010
ISSN: 0893-133X
DOI: 10.1038/npp.2010.122

Record 13 of 183

Author(s): Pilhatsch, M (Pilhatsch, Maximilian); Wolf, R (Wolf, Roland); Winter, C (Winter, Christine); Lewitzka, U (Lewitzka, Ute); Bauer, M (Bauer, Michael)

Title: Comparison of paroxetine and amitriptyline as adjunct to lithium maintenance therapy in bipolar depression: A reanalysis of a randomized, double-blind study

Source: JOURNAL OF AFFECTIVE DISORDERS, 126 (3): 453-457 NOV 2010

ISSN: 0165-0327

DOI: 10.1016/j.jad.2010.04.025

Record 14 of 183

Author(s): Vieta, E (Vieta, Eduard); Locklear, J (Locklear, Julie); Gunther, O (Guenther, Oliver); Ekman, M (Ekman, Mattias); Miltenburger, C (Miltenburger, Carolin); Chatterton, ML (Chatterton, Mary Lou); Astrom, M (Astrom, Mikael); Paulsson, B (Paulsson, Bjorn)

Title: Treatment Options for Bipolar Depression A Systematic Review of Randomized, Controlled Trials

Source: JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, 30 (5): 579-590 OCT 2010

ISSN: 0271-0749

DOI: 10.1097/JCP.0b013e3181f15849

Record 15 of 183

Author(s): El-Mallakh, RS (El-Mallakh, Rif S.); Penagaluri, P (Penagaluri, Praveen); Kantamneni, A (Kantamneni, Arun); Gao, Y (Gao, Yonglin); Roberts, RJ (Roberts, Rona J.)

Title: Long-Term Use of Pramipexole in Bipolar Depression: A Naturalistic Retrospective Chart Review

Source: PSYCHIATRIC QUARTERLY, 81 (3): 207-213 SEP 2010

ISSN: 0033-2720

DOI: 10.1007/s11126-010-9130-6

Record 16 of 183

Author(s): van der Loos, MLM (van der Loos, M. L. M.); Mulder, P (Mulder, P.); Hartong, EGTM (Hartong, E. G. Th. M.); Blom, MBJ (Blom, M. B. J.); Vergouwen, AC (Vergouwen, A. C.); van Noorden, MS (van Noorden, M. S.); Timmermans, MA (Timmermans, M. A.); Vieta, E (Vieta, E.); Nolen, WA (Nolen, W. A.)

Group Author(s): LamLit Study Grp

Title: Efficacy and safety of two treatment algorithms in bipolar depression consisting of a combination of lithium, lamotrigine or placebo and paroxetine

Source: ACTA PSYCHIATRICA SCANDINAVICA, 122 (3): 246-254 SEP 2010

ISSN: 0001-690X

DOI: 10.1111/j.1600-0447.2009.01537.x

Record 17 of 183

Author(s): Lee, HJ (Lee, H-J); Rao, JS (Rao, J. S.); Chang, L (Chang, L.); Rapoport, SI (Rapoport, S. I.); Kim, HW (Kim, H-W)

Title: Chronic imipramine but not bupropion increases arachidonic acid signaling in rat brain: is this related to 'switching' in bipolar disorder?

Source: MOLECULAR PSYCHIATRY, 15 (6): 602-614 JUN 2010

ISSN: 1359-4184

DOI: 10.1038/mp.2008.117

Record 18 of 183

Author(s): Tondo, L (Tondo, L.); Vazquez, G (Vazquez, G.); Baldessarini, RJ (Baldessarini, R. J.)

Title: Mania associated with antidepressant treatment: comprehensive meta-analytic review

Source: ACTA PSYCHIATRICA SCANDINAVICA, 121 (6): 404-414 JUN 2010

ISSN: 0001-690X

DOI: 10.1111/j.1600-0447.2009.01514.x

Record 19 of 183

Author(s): Baldessarini, RJ (Baldessarini, Ross J.); Vieta, E (Vieta, Eduard); Calabrese, JR (Calabrese, Joseph R.); Tohen, M (Tohen, Mauricio); Bowden, CL (Bowden, Charles L.)

Title: Bipolar Depression: Overview and Commentary

Source: HARVARD REVIEW OF PSYCHIATRY, 18 (3): 143-157 JUN 2010

ISSN: 1067-3229

Record 20 of 183

Author(s): Parikh, SV (Parikh, Sagar V.); LeBlanc, SR (LeBlanc, Serge R.); Ovanessian, MM (Ovanessian, Melina M.)

Title: Advancing Bipolar Disorder: Key Lessons From the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

Source: CANADIAN JOURNAL OF PSYCHIATRY-REVUE CANADIENNE DE PSYCHIATRIE, 55 (3): 136-143 MAR 2010

ISSN: 0706-7437

Record 21 of 183

Author(s): Pringuey, D (Pringuey, D.); Cherikh, F (Cherikh, F.); Tible, O (Tible, O.); Giordana, B (Giordana, B.)

Title: Treatment of a first depressive episode in bipolar disorder

Source: ENCEPHALE-REVUE DE PSYCHIATRIE CLINIQUE BIOLOGIQUE ET THERAPEUTIQUE, 36: S27-S33 Suppl. 1 JAN 2010

ISSN: 0013-7006

Record 22 of 183

Author(s): Grunze, H (Grunze, Heinz); Vieta, E (Vieta, Eduard); Goodwin, GM (Goodwin, Guy M.); Bowden, C (Bowden, Charles); Licht, RW (Licht, Rasmus W.); Moller, HJ (Moeller, Hans-Juergen); Kasper, S (Kasper, Siegfried)

Group Author(s): WFSBP Task Force Treatment Guideli

Title: The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: Update 2010 on the treatment of acute bipolar depression

Source: WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY, 11 (2): 81-109 MAR 2010

ISSN: 1562-2975

DOI: 10.3109/15622970903555881

Record 23 of 183

Author(s): Ansari, A (Ansari, Arash); Osser, DN (Osser, David N.)

Title: The Psychopharmacology Algorithm Project at the Harvard South Shore Program: An Update on Bipolar Depression

Source: HARVARD REVIEW OF PSYCHIATRY, 18 (1): 36-55 JAN-FEB 2010

ISSN: 1067-3229

DOI: 10.3109/10673220903523524

Record 24 of 183

Author(s): Baldassano, C (Baldassano, Claudia)

Title: PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER

Source: CNS SPECTRUMS, 15 (2): 10-13 Suppl. 3 FEB 2010

ISSN: 1092-8529

Record 25 of 183

Author(s): Taylor, E (Taylor, Eric)

Title: Managing bipolar disorders in children and adolescents

Source: NATURE REVIEWS NEUROLOGY, 5 (9): 484-491 SEP 2009

ISSN: 1759-4758

DOI: 10.1038/nrneurol.2009.117

Record 26 of 183

Author(s): Young, AH (Young, Allan H.); McElroy, SL (McElroy, Susan L.); Bauer, M (Bauer, Michael); Philips, N (Philips, Nabil); Chang, W (Chang, William); Olausson, B (Olausson, Bengt); Paulsson, B (Paulsson, Bjoern); Brecher, M (Brecher, Martin)

Group Author(s): EMBOLDEN I Trial 001 Investigators

Title: A Double-Blind, Placebo-Controlled Study of Quetiapine and Lithium Monotherapy in Adults in the Acute Phase of Bipolar Depression (EMBOLDEN I)

Source: JOURNAL OF CLINICAL PSYCHIATRY, 71 (2): 150-162 FEB 2010

ISSN: 0160-6689

DOI: 10.4088/JCP.08m04995gre

Record 27 of 183

Author(s): McElroy, SL (McElroy, Susan L.); Weisler, RH (Weisler, Richard H.); Chang, W (Chang, William); Olausson, B (Olausson, Bengt); Paulsson, B (Paulsson, Bjoern); Brecher, M (Brecher, Martin); Agambaram, V (Agambaram, Vasavan); Merideth, C (Merideth, Charles); Nordenhem, A (Nordenhem, Arvid); Young, AH (Young, Allan H.)

Group Author(s): EMBOLDEN II Trial D1447C00134 Inve

Title: A Double-Blind, Placebo-Controlled Study of Quetiapine and Paroxetine as Monotherapy in Adults With Bipolar Depression (EMBOLDEN II)

Source: JOURNAL OF CLINICAL PSYCHIATRY, 71 (2): 163-174 FEB 2010

ISSN: 0160-6689

DOI: 10.4088/JCP.08m04942gre

Record 28 of 183

Author(s): Valiengo, LDL (Lane Valiengo, Leandro da Costa); de Jesus, LP (de Jesus, Leonardo Peroni); Zanetti, MV (Zanetti, Marcus Vinicius)

Title: Antidepressants in bipolar depression: risk versus efficacy

Source: REVISTA DE PSIQUIATRIA CLINICA, 36 (6): 248-249 2009

ISSN: 0101-6083

Record 29 of 183

Author(s): Hirschfeld, RMA (Hirschfeld, Robert M. A.)

Title: Making efficacious choices: the integration of pharmacotherapy and nonpharmacologic approaches to the treatment of patients with bipolar disorder

Source: ANNALS OF CLINICAL PSYCHIATRY, 21 (4): S6-S11 Suppl. S NOV 2009

ISSN: 1040-1237

Record 30 of 183

Author(s): Yatham, LN (Yatham, Lakshmi N.)

Title: Is Monotherapy as Good as Polypharmacy for BD?

Source: CANADIAN JOURNAL OF PSYCHIATRY-REVUE CANADIENNE DE PSYCHIATRIE, 54 (11): 724-725 NOV 2009

ISSN: 0706-7437

Record 31 of 183

Author(s): Malhi, GS (Malhi, Gin S.); Adams, D (Adams, Danielle); Cahill, CM (Cahill, Catherine M.); Dodd, S (Dodd, Seetal); Berk, M (Berk, Michael)

Title: The Management of Individuals with Bipolar Disorder A Review of the Evidence and its Integration into Clinical Practice

Source: DRUGS, 69 (15): 2063-2101 2009

ISSN: 0012-6667

Record 32 of 183

Author(s): Malhi, GS (Malhi, Gin S.); Adams, D (Adams, Danielle); Berk, M (Berk, Michael)

Title: Medicating mood with maintenance in mind: bipolar depression pharmacotherapy

Source: BIPOLAR DISORDERS, 11: 55-76 Suppl. 2 JUN 2009

ISSN: 1398-5647

Record 33 of 183

Author(s): Peritogiannis, V (Peritogiannis, V.); Antoniou, K (Antoniou, K.); Mouka, V (Mouka, V.); Mavreas, V (Mavreas, V.); Hyphantis, TN (Hyphantis, T. N.)

Title: Duloxetine-induced hypomania: case report and brief review of the literature on SNRIs-induced mood switching

Source: JOURNAL OF PSYCHOPHARMACOLOGY, 23 (5): 592-596 JUL 2009

ISSN: 0269-8811

DOI: 10.1177/0269881108089841

Record 34 of 183

Author(s): Quante, A (Quante, A.); van Hall, F (van Hall, F.); Anghelescu, I (Anghelescu, I.)

Title: Psychopharmacological Combination Therapy in Bipolar Disorder

Source: FORTSCHRITTE DER NEUROLOGIE PSYCHIATRIE, 77 (5): 252-262 MAY 2009

ISSN: 0720-4299

DOI: 10.1055/s-0028-1109324

Record 35 of 183

Author(s): Altshuler, LL (Altshuler, Lori L.); Post, RM (Post, Robert M.); Hellemann, G (Hellemann, Gerhard); Leverich, GS (Leverich, Gabriele S.); Nolen, WA (Nolen, Willem A.); Frye, MA (Frye, Mark A.); Keck, PE (Keck, Paul E., Jr.); Kupka, RW (Kupka, Ralph W.); Grunze, H (Grunze, Heinz); McElroy, SL (McElroy, Susan L.); Sugar, CA (Sugar, Catherine A.); Suppes, T (Suppes, Trisha)

Title: Impact of Antidepressant Continuation After Acute Positive or Partial Treatment Response for Bipolar Depression: A Blinded, Randomized Study

Source: JOURNAL OF CLINICAL PSYCHIATRY, 70 (4): 450-457 APR 2009

ISSN: 0160-6689

Record 36 of 183

Author(s): Grandjean, EM (Grandjean, Etienne Marc); Aubry, JM (Aubry, Jean-Michel)

Title: Lithium: Updated Human Knowledge Using an Evidence-Based Approach Part I: Clinical Efficacy in Bipolar Disorder

Source: CNS DRUGS, 23 (3): 225-240 2009

ISSN: 1172-7047

Record 37 of 183

Author(s): Malhi, GS (Malhi, G. S.); Adams, D (Adams, D.); Lampe, L (Lampe, L.); Paton, M (Paton, M.); O'Connor, N (O'Connor, N.); Newton, LA (Newton, L. A.); Walter, G (Walter, G.); Taylor, A (Taylor, A.); Porter, R (Porter, R.); Mulder, RT (Mulder, R. T.); Berk, M (Berk, M.)

Title: Clinical practice recommendations for bipolar disorder

Source: ACTA PSYCHIATRICA SCANDINAVICA, 119: 27-46 Suppl. 439 MAY 2009

ISSN: 0001-690X

DOI: 10.1111/j.1600-0447.2009.01383.x

Record 38 of 183

Author(s): Koukopoulos, A (Koukopoulos, Athanasios); Ghaemi, SN (Ghaemi, S. Nassir)

Title: The primacy of mania: A reconsideration of mood disorders

Source: EUROPEAN PSYCHIATRY, 24 (2): 125-134 MAR 2009

ISSN: 0924-9338

DOI: 10.1016/j.eurpsy.2008.07.006

Record 39 of 183

Author(s): Goldberg, JF (Goldberg, Joseph F.); Brooks, JO (Brooks, John O.); Kurita, K (Kurita, Keiko); Hoblyn, JC (Hoblyn, Jennifer C.); Ghaemi, N (Ghaemi, Nassir); Perlis, RH (Perlis, Roy H.); Miklowitz, DJ (Miklowitz, David J.); Ketter, TA (Ketter, Terence A.); Sachs, GS (Sachs, Gary S.); Thase, ME (Thase, Michael E.)

Title: Depressive Illness Burden Associated With Complex Polypharmacy in Patients With Bipolar Disorder: Findings From the STEP-BD

Source: JOURNAL OF CLINICAL PSYCHIATRY, 70 (2): 155-162 FEB 2009

ISSN: 0160-6689

Record 40 of 183

Author(s): van der Loos, MLM (van der Loos, Marc L. M.); Mulder, PGH (Mulder, Paul G. H.); Hartong, EGTM (Hartong, Erwin G. Th. M.); Blom, MBJ (Blom, Marc B. J.); Vergouwen, AC (Vergouwen, Anton C.); de Keyzer, HJUEM (de Keyzer, Herman J. U. E. M.); Notten, PJH (Notten, Peter J. H.); Luteijn, ML (Luteijn, Marijke L.); Timmermans, MA (Timmermans, Manuela A.); Nolen, WA (Nolen, Willem A.)

Group Author(s): Vieta, E

Title: Efficacy and Safety of Lamotrigine as Add-On Treatment to Lithium in Bipolar Depression: A Multicenter, Double-Blind, Placebo-Controlled Trial

Source: JOURNAL OF CLINICAL PSYCHIATRY, 70 (2): 223-231 FEB 2009

ISSN: 0160-6689

Record 41 of 183

Author(s): Azorin, JM (Azorin, Jean-Michel); Kaladjian, A (Kaladjian, Arthur)

Title: An update on the treatment of bipolar depression

Source: EXPERT OPINION ON PHARMACOTHERAPY, 10 (2): 161-172 FEB 2009

ISSN: 1465-6566

DOI: 10.1517/14656560802653172

Record 42 of 183

Author(s): Goldberg, JF (Goldberg, Joseph F.); Perlis, RH (Perlis, Roy H.); Bowden, CL (Bowden, Charles L.); Thase, ME (Thase, Michael E.); Miklowitz, DJ (Miklowitz, David J.); Marangell, LB (Marangell, Lauren B.); Calabrese, JR (Calabrese, Joseph R.); Nierenberg, AA (Nierenberg, Andrew A.); Sachs, GS (Sachs, Gary S.)

Title: Manic Symptoms During Depressive Episodes in 1,380 Patients With Bipolar Disorder: Findings From the STEP-BD

Source: AMERICAN JOURNAL OF PSYCHIATRY, 166 (2): 173-181 FEB 2009

ISSN: 0002-953X

DOI: 10.1176/appi.ajp.2008.08050746

Record 43 of 183

Author(s): EI-Mallakh, RS (EI-Mallakh, Rif S.); Ghaemi, SN (Ghaemi, S. Nassir); Sagduyu, K (Sagduyu, Kemal); Thase, ME (Thase, Michael E.); Wisniewski, SR (Wisniewski, Stephen R.); Nierenberg, AA (Nierenberg, Andrew A.); Zhang, HW (Zhang, Hong Wei); Pardo, TA (Pardo, Tamara A.); Sachs, G (Sachs, Gary)

Group Author(s): STEP-BD Investigators

Title: Antidepressant-associated chronic irritable dysphoria (ACID) in STEP-BD patients

Source: JOURNAL OF AFFECTIVE DISORDERS, 111 (2-3): 372-377 DEC 2008

ISSN: 0165-0327

DOI: 10.1016/j.jad.2008.03.025

Record 44 of 183

Author(s): Birkenhager, TK (Birkenhager, Tom K.); van den Broek, WW (van den Broek, Walter W.); Moleman, P (Moleman, Peter); Bruijn, JA (Bruijn, Jan A.)

Title: Reply to Dr Baldessarini's Comments on "Efficacy of Imipramine in Psychotic Versus Nonpsychotic Depression"

Source: JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, 28 (6): 717-718 DEC 2008

ISSN: 0271-0749

Record 45 of 183

Author(s): Nierenberg, AA (Nierenberg, Andrew A.)

Title: An Analysis of the Efficacy of Treatments for Bipolar Depression

Source: JOURNAL OF CLINICAL PSYCHIATRY, 69: 4-8 Suppl. 5 2008

ISSN: 0160-6689

Record 46 of 183

Author(s): Ketter, TA (Ketter, Terence A.)

Title: Monotherapy Versus Combined Treatment With Second-Generation Antipsychotics in Bipolar Disorder

Source: JOURNAL OF CLINICAL PSYCHIATRY, 69: 9-15 Suppl. 5 2008

ISSN: 0160-6689

Record 47 of 183

Author(s): Marks, DM (Marks, David M.); Park, MH (Park, Min-Hyeon); Ham, BJ (Ham, Byung-Joo); Han, C (Han, Changsu); Patkar, AA (Patkar, Ashwin A.); Masand, PS (Masand, Prakash S.); Pae, CU (Pae, Chi-Un)

Title: Paroxetine: safety and tolerability issues

Source: EXPERT OPINION ON DRUG SAFETY, 7 (6): 783-794 NOV 2008

ISSN: 1474-0338

DOI: 10.1517/14740330802423168

Record 48 of 183

Author(s): Ghaemi, S (Nassir Ghaemi, S.)

Title: Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression

Source: BIPOLAR DISORDERS, 10 (8): 957-968 DEC 2008

ISSN: 1398-5647

DOI: 10.1111/j.1399-5618.2008.00639.x

Record 49 of 183

Author(s): Wilting, I (Wilting, I.); Souverein, PC (Souverein, P. C.); Nolen, WA (Nolen, W. A.); Egberts, ACG (Egberts, A. C. G.); Heerdink, ER (Heerdink, E. R.)

Title: Changes in outpatient lithium treatment in the Netherlands during 1996-2005

Source: JOURNAL OF AFFECTIVE DISORDERS, 111 (1): 94-99 NOV 2008

ISSN: 0165-0327

DOI: 10.1016/j.jad.2008.01.019

Record 50 of 183

Author(s): Fountoulakis, KN (Fountoulakis, Konstantinos N.); Vieta, E (Vieta, Eduard)

Title: Treatment of bipolar disorder: a systematic review of available data and clinical perspectives

Source: INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY, 11 (7): 999-1029 NOV 2008

ISSN: 1461-1457
DOI: 10.1017/S1461145708009231

Record 51 of 183

Author(s): Ghaemi, SN (Ghaemi, S. N.); Wingo, AP (Wingo, A. P.); Filkowski, MA (Filkowski, M. A.); Baldessarini, RJ (Baldessarini, R. J.)

Title: Long-term antidepressant treatment in bipolar disorder: meta-analyses of benefits and risks

Source: ACTA PSYCHIATRICA SCANDINAVICA, 118 (5): 347-356 NOV 2008
ISSN: 0001-690X
DOI: 10.1111/j.1600-0447.2008.01257.x

Record 52 of 183

Author(s): Fountoulakis, KN (Fountoulakis, Konstantinos N.)

Title: The contemporary face of bipolar illness: Complex diagnostic and therapeutic challenges

Source: CNS SPECTRUMS, 13 (9): 763-+ SEP 2008
ISSN: 1092-8529

Record 53 of 183

Author(s): Salvi, V (Salvi, Virginio); Fagiolini, A (Fagiolini, Andrea); Swartz, HA (Swartz, Holly A.); Maina, G (Maina, Giuseppe); Frank, E (Frank, Ellen)

Title: The use of antidepressants in bipolar disorder

Source: JOURNAL OF CLINICAL PSYCHIATRY, 69 (8): 1307-1318 AUG 2008
ISSN: 0160-6689

Record 54 of 183

Author(s): Harel, EV (Harel, Eiran Vadim); Levkovitz, Y (Levkovitz, Yechiel)

Title: Effectiveness and safety of adjunctive antidepressants in the treatment of bipolar depression: A review

Source: ISRAEL JOURNAL OF PSYCHIATRY AND RELATED SCIENCES, 45 (2): 121-128 2008
ISSN: 0333-7308

Record 55 of 183

Author(s): Smith, DJ (Smith, D. J.); Ghaemi, SN (Ghaemi, S. N.); Craddock, N (Craddock, N.)

Title: The broad clinical spectrum of bipolar disorder: implications for research and practice

Source: JOURNAL OF PSYCHOPHARMACOLOGY, 22 (4): 397-400 JUN 2008
ISSN: 0269-8811
DOI: 10.1177/0269881108089585

Record 56 of 183

Author(s): Goldberg, JF (Goldberg, J. F.)

Title: On being bipolar without being bipolar

Source: JOURNAL OF PSYCHOPHARMACOLOGY, 22 (4): 402-403 JUN 2008
ISSN: 0269-8811
DOI: 10.1177/0269881108092123

Record 57 of 183

Author(s): Goodwin, GM (Goodwin, Guy M.); Anderson, I (Anderson, Ian); Arango, C (Arango, Celso); Bowden, CL (Bowden, Charles L.); Henry, C (Henry, Chantal); Mitchell, PB (Mitchell, Philip B.); Nolen, WA (Nolen, Willem A.); Vieta, E (Vieta, Eduard); Wittchen, HU (Wittchen, Hans-Ulrich)

Title: ECNP consensus meeting. Bipolar depression. Nice, March 2007

Source: EUROPEAN NEUROPSYCHOPHARMACOLOGY, 18 (7): 535-549 JUL 2008

ISSN: 0924-977X

DOI: 10.1016/j.euroneuro.2008.03.003

Record 58 of 183

Author(s): Fountoulakis, KN (Fountoulakis, Konstantinos N.); Grunze, H (Grunze, Heinz); Panagiotidis, P (Panagiotidis, Panagiotis); Kaprinis, G (Kaprinis, George)

Title: Treatment of bipolar depression: An update

Source: JOURNAL OF AFFECTIVE DISORDERS, 109 (1-2): 21-34 JUL 2008

ISSN: 0165-0327

DOI: 10.1016/j.jad.2007.10.016

Record 59 of 183

Author(s): Beyer, JL (Beyer, John L.)

Title: An evidence-based medicine strategy for achieving remission in bipolar disorder

Source: JOURNAL OF CLINICAL PSYCHIATRY, 69: 31-37 Suppl. 3 2008

ISSN: 0160-6689

Record 60 of 183

Author(s): Motohashi, N (Motohashi, Nobutaka); Shioe, K (Shioe, Kunihiko); Nakamura, J (Nakamura, Jun); Ohshima, A (Ohshima, Akihiko); Yamada, K (Yamada, Kazuo); Ozawa, H (Ozawa, Hiroki); Someya, T (Someya, Toshiyuki); Uchitomi, Y (Uchitomi, Ysuke); Higuchi, T (Higuchi, Teruhiko)

Title: Revised psychopharmacological algorithms for the treatment of mood disorders in Japan

Source: INTERNATIONAL JOURNAL OF PSYCHIATRY IN CLINICAL PRACTICE, 12 (1): 11-18 MAR 2008

ISSN: 1365-1501

DOI: 10.1080/13651500701330791

Record 61 of 183

Author(s): Pfennig, A (Pfennig, Andrea); Sasse, J (Sasse, Johanna); Bauer, M (Bauer, Michael)

Title: Mood-Stabilizer, antidepressants and atypical antipsychotics for bipolar depression

Source: PSYCHOPHARMAKOTHERAPIE, 15 (1): 20-24 Suppl. 18 JAN-FEB 2008

ISSN: 0944-6877

Record 62 of 183

Author(s): Xia, GH (Xia, Guohua); Gajwani, P (Gajwani, Prashant); Muzina, DJ (Muzina, David J.); Kemp, DE (Kemp, David E.); Gao, K (Gao, Keming); Ganocy, SJ (Ganocy, Stephen J.); Calabrese, JR (Calabrese, Joseph R.)

Title: Treatment-emergent mania in unipolar and bipolar depression: focus on repetitive transcranial magnetic stimulation

Source: INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY, 11 (1): 119-130 FEB 2008

ISSN: 1461-1457

DOI: 10.1017/S1461145707007699

Record 63 of 183

Author(s): Hausmann, A (Hausmann, Armand); Fuchs, M (Fuchs, Martin); Walpoth, M (Walpoth, Michaela); Hortnagl, C (Hoertnagl, Christine); Adami, P (Adami, Petra); Conca, A (Conca, Andreas)

Title: Are there substantial reasons for contraindicating antidepressants in bipolar disorder? Part III. The alternatives!

Source: NEUROPSYCHIATRIE, 21 (4): 248-260 2007

ISSN: 0948-6259

Record 64 of 183

Author(s): Keck, PE (Keck, Paul E., Jr.); McIntyre, RS (McIntyre, Roger S.); Shelton, RC (Shelton, Richard C.)

Title: Case studies in bipolar depression: Best practices for the outpatient

Source: CNS SPECTRUMS, 12 (12): 4-+ Suppl. 20 DEC 2007

ISSN: 1092-8529

Record 65 of 183

Author(s): Goldberg, JF (Goldberg, Joseph F.)

Title: What constitutes evidence-based pharmacotherapy for bipolar disorder? Part 1: First-line treatments

Source: JOURNAL OF CLINICAL PSYCHIATRY, 68 (12): 1982-1983 DEC 2007

ISSN: 0160-6689

Record 66 of 183

Author(s): Carlson, GA (Carlson, Gabrielle A.); Finch, SJ (Finch, Stephen J.); Fochtmann, LJ (Fochtmann, Laura J.); Ye, Q (Ye, Qing); Wang, Q (Wang, Qing); Naz, B (Naz, Bushra); Bromet, EJ (Bromet, Evelyn J.)

Title: Antidepressant-associated switches from depression to mania in severe bipolar disorder

Source: BIPOLAR DISORDERS, 9 (8): 851-859 DEC 2007

ISSN: 1398-5647

Record 67 of 183

Author(s): Papakostas, GI (Papakostas, George I.)

Title: Limitations of contemporary antidepressants: Tolerability

Source: JOURNAL OF CLINICAL PSYCHIATRY, 68: 11-17 Suppl. 10 2007

ISSN: 0160-6689

Record 68 of 183

Author(s): Oswald, P (Oswald, Pierre); Souery, D (Souery, Daniel); Kasper, S (Kasper, Siegfried); Lecrubier, Y (Lecrubier, Yves); Montgomery, S (Montgomery, Stuart); Wyckaert, S (Wyckaert, Sabien); Zohar, J (Zohar, Joseph); Mendlewicz, J (Mendlewicz, Julien)

Title: Current issues in bipolar disorder: A critical review

Source: EUROPEAN NEUROPSYCHOPHARMACOLOGY, 17 (11): 687-695 NOV 2007

ISSN: 0924-977X

DOI: 10.1016/j.euroneuro.2007.03.006

Record 69 of 183

Author(s): Calabrese, JR (Calabrese, Joseph R.); Guelfi, JD (Guelfi, Julien Daniel); Perdrizet-Chevallier, C (Perdrizet-Chevallier, Catherine)

Group Author(s): Agomelatine Bipolar Study Grp

Title: Agomelatine adjunctive therapy for acute bipolar depression: preliminary open data

Source: BIPOLAR DISORDERS, 9 (6): 628-635 SEP 2007

ISSN: 1398-5647

Record 70 of 183

Author(s): Frye, MA (Frye, Mark A.); Grunze, H (Grunze, Heinz); Suppes, T (Suppes, Trisha); McElroy, SL (McElroy, Susan L.); Keck, PE (Keck, Paul E.); Walden, J (Walden, Jorge); Leverich, GS (Leverich, Gabriele S.); Altshuler, LL (Altshuler, Lori L.); Nakelsky, S (Nakelsky, Shoshanna); Hwang, S (Hwang, Sun); Mintz, J (Mintz, Jim); Post, RM (Post, Robert M.)

Title: A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression

Source: AMERICAN JOURNAL OF PSYCHIATRY, 164 (8): 1242-1249 AUG 2007

ISSN: 0002-953X

DOI: 10.1176/appi.ajp.2007.06060981

Record 71 of 183

Author(s): Strakowski, SM (Strakowski, Stephen M.)

Title: Approaching the challenge of bipolar depression: Results from STEP-BD

Source: AMERICAN JOURNAL OF PSYCHIATRY, 164 (9): 1301-1303 SEP 2007

ISSN: 0002-953X

DOI: 10.1176/appi.ajp.2007.07060926

Record 72 of 183

Author(s): Goldberg, JF (Goldberg, Joseph F.); Perlis, RH (Perlis, Roy H.); Ghaerni, SN (Ghaerni, S. Nassir); Calabrese, JR (Calabrese, Joseph R.); Bowden, CL (Bowden, Charles L.); Wisniewski, S (Wisniewski, Stephen); Miklowitz, DJ (Miklowitz, David J.); Sachs, GS (Sachs, Gary S.); Thase, ME (Thase, Michael E.)

Title: Adjunctive antidepressant use and symptomatic recovery among bipolar depressed patients with concomitant manic symptoms: Findings from the STEP-BD

Source: AMERICAN JOURNAL OF PSYCHIATRY, 164 (9): 1348-1355 SEP 2007

ISSN: 0002-953X

Record 73 of 183

Author(s): El-Mallakh, RS (El-Mallakh, Rif S.)

Title: Adjunctive antidepressant treatment for bipolar depression

Source: NEW ENGLAND JOURNAL OF MEDICINE, 357 (6): 615-615 AUG 9 2007

ISSN: 0028-4793

Record 74 of 183

Author(s): Hausmann, A (Hausmann, Armand); Hoertnagl, C (Hoertnagl, Christine); Walpoth, M (Walpoth, Michaela); Fuchs, M (Fuchs, Martin); Conca, A (Conca, Andreas)

Title: Are there substantial reasons for contraindicating antidepressants in bipolar disorder? Part II: Facts or artefacts?

Source: NEUROPSYCHIATRIE, 21 (2): 131-158 2007

ISSN: 0948-6259

Record 75 of 183

Author(s): Cousins, DA (Cousins, David A.); Young, AH (Young, Allan H.)

Title: The armamentarium of treatments for bipolar disorder: a review of the literature

Source: INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY, 10 (3): 411-431 JUN 2007

ISSN: 1461-1457

DOI: 10.1017/S1461145706007413

Record 76 of 183

Author(s): Goldberg, JF (Goldberg, Joseph F.)

Title: What psychotherapists should know about pharmacotherapies for bipolar disorder

Source: JOURNAL OF CLINICAL PSYCHOLOGY, 63 (5): 475-490 MAY 2007

ISSN: 0021-9762

DOI: 10.1002/jclp.20362

Record 77 of 183

Author(s): Sachs, GS (Sachs, Gary S.); Nierenberg, AA (Nierenberg, Andrew A.); Calabrese, JR (Calabrese, Joseph R.); Marangell, LB (Marangell, Lauren B.); Wisniewski, SR (Wisniewski, Stephen R.); Gyulai, L (Gyulai, Laszlo); Friedman, ES (Friedman, Edward S.); Bowden, CL (Bowden, Charles L.); Fossey, MD (Fossey, Mark D.); Ostacher, MJ (Ostacher, Michael J.); Ketter, TA (Ketter, Terence A.); Patel, J (Patel, Jayendra); Hauser, P (Hauser, Peter); Rapport, D (Rapport, Daniel); Martinez, JM (Martinez, James M.); Allen, MH (Allen, Michael H.); Miklowitz, DJ (Miklowitz, David J.); Otto, MW (Otto, Michael W.); Dennehy, EB (Dennehy, Ellen

B.); Thase, ME (Thase, Michael E.)

Title: Effectiveness of adjunctive antidepressant treatment for bipolar depression

Source: NEW ENGLAND JOURNAL OF MEDICINE, 356 (17): 1711-1722 APR 26 2007

ISSN: 0028-4793

DOI: 10.1056/NEJMoa064135

Record 78 of 183

Author(s): Drieling, T (Drieling, T.); Biedermann, NC (Biedermann, N. C.); Schaerer, LO (Schaerer, L. O.); Strobl, N (Strobl, N.); Langosch, JM (Langosch, J. M.)

Title: Psychotropic drug-induced change of weight: A review

Source: FORTSCHRITTE DER NEUROLOGIE PSYCHIATRIE, 75 (2): 65-80 FEB 2007

ISSN: 0720-4299

DOI: 10.1055/s-2005.919109

Record 79 of 183

Author(s): Marmol, F (Marmol, Frederic)

Title: Vigency of lithium treatment - Authors' reply

Source: MEDICINA CLINICA, 128 (1): 36-37 JAN 13 2007

ISSN: 0025-7753

Record 80 of 183

Author(s): Goodnick, PJ (Goodnick, Paul J.)

Title: Bipolar depression: a review of randomised clinical trials

Source: EXPERT OPINION ON PHARMACOTHERAPY, 8 (1): 13-21 JAN 2007

ISSN: 1465-6566

DOI: 10.1517/14656566.7.1.13

Record 81 of 183

Author(s): Wilson, MS (Wilson, Michael S.); Findling, RL (Findling, Robert L.)

Title: Zonisamide for bipolar depression

Source: EXPERT OPINION ON PHARMACOTHERAPY, 8 (1): 111-113 JAN 2007

ISSN: 1465-6566

DOI: 10.1517/14656566.8.1.111

Record 82 of 183

Author(s): Thuile, J (Thuile, J.); Even, C (Even, C.); Guelfi, JD (Guelfi, J. D.)

Title: Bipolar depression: a review of current therapeutic strategies

Source: ENCEPHALE-REVUE DE PSYCHIATRIE CLINIQUE BIOLOGIQUE ET THERAPEUTIQUE, 32 (5): 767-774 Part 1 SEP-OCT 2006

ISSN: 0013-7006

Record 83 of 183

Author(s): Tamada, RS (Tamada, Renata Sayuri); Amaral, JA (Amaral, Jose Antonio); Issler, CK (Issler, Cilly Kluger); Nierenberg, AA (Nierenberg, Andrew Alan); Lafer, B (Lafer, Beny)

Title: Antidepressant treatment-emergent affective switch in bipolar disorder: a prospective case-control study of outcome

Source: REVISTA BRASILEIRA DE PSIQUIATRIA, 28 (4): 297-300 DEC 2006

ISSN: 1516-4446

Record 84 of 183

Author(s): Singh, JB (Singh, Jaskaran B.); Zarate, CA (Zarate, Carlos A., Jr.)

Title: Pharmacological treatment of psychiatric comorbidity in bipolar disorder: a review of controlled trials

Source: BIPOLAR DISORDERS, 8 (6): 696-709 DEC 2006

ISSN: 1398-5647

Record 85 of 183

Author(s): Thase, ME (Thase, Michael E.); Macfadden, W (Macfadden, Wayne); Weisler, RH (Weisler, Richard H.); Chang, W (Chang, William); Paulsson, B (Paulsson, Bjorn); Khan, A (Khan, Arifulla); Calabrese, JR (Calabrese, Joseph R.)

Group Author(s): BOLDER II Study Grp

Title: Efficacy of quetiapine monotherapy in bipolar I and II depression - A double-blind, placebo-controlled study (The BOLDER II study)

Source: JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, 26 (6): 600-609 DEC 2006

ISSN: 0271-0749

DOI: 10.1097/01.jcp.0000248603.76231.b7

Record 86 of 183

Author(s): Schaffer, A (Schaffer, Ayal); Zuker, P (Zuker, Pamela); Levitt, A (Levitt, Anthony)

Title: Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression

Source: JOURNAL OF AFFECTIVE DISORDERS, 96 (1-2): 95-99 NOV 2006

ISSN: 0165-0327

DOI: 10.1016/j.jad.2006.05.023

Record 87 of 183

Author(s): Thase, ME (Thase, Michael E.)

Title: Bipolar depression: Diagnostic and treatment considerations

Source: DEVELOPMENT AND PSYCHOPATHOLOGY, 18 (4): 1213-1230 FAL 2006

ISSN: 0954-5794

DOI: 10.1017/S0954579406060585

Record 88 of 183

Author(s): Manwani, SG (Manwani, Sumita G.); Pardo, TB (Pardo, Tamara B.); Albanese, MJ (Albanese, Mark J.); Zablotsky, B (Zablotsky, Benjamin); Goodwin, FK (Goodwin, Frederick K.); Ghaemi, SN (Ghaemi, S. Nassir)

Title: Substance use disorder and other predictors of antidepressant-induced mania: A retrospective chart review

Source: JOURNAL OF CLINICAL PSYCHIATRY, 67 (9): 1341-1345 SEP 2006

ISSN: 0160-6689

Record 89 of 183

Author(s): McElroy, SL (McElroy, Susan L.); Kotwal, R (Kotwal, Renu); Kaneria, R (Kaneria, Rakesh); Keck, PE (Keck, Paul E., Jr.)

Title: Antidepressants and suicidal behavior in bipolar disorder

Source: BIPOLAR DISORDERS, 8 (5): 596-617 Part 2 OCT 2006

ISSN: 1398-5647

Record 90 of 183

Author(s): Ostacher, MJ (Ostacher, Michael J.)

Title: The evidence for antidepressant use in bipolar depression

Source: JOURNAL OF CLINICAL PSYCHIATRY, 67: 18-21 Suppl. 11 2006

ISSN: 0160-6689

Record 91 of 183

Author(s): Post, RM (Post, R. M.); Altshuler, LL (Altshuler, L. L.); Leverich, GS (Leverich, G. S.); Frye, MA (Frye, M. A.); Nolen, WA (Nolen, W. A.); Kupka, RW (Kupka, R. W.); Suppes, T (Suppes, T.); McElroy, S (McElroy, S.); Keck, PE (Keck, P. E.); Denicoff, KD (Denicoff, K. D.); Grunze, H (Grunze, H.); Kitchen, CMR (Kitchen, C. M. R.); Mintz, J (Mintz, J.)

Title: Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline

Source: BRITISH JOURNAL OF PSYCHIATRY, 189: 124-131 AUG 2006

ISSN: 0007-1250

Record 92 of 183

Author(s): El-Mallakh, RS (El-Mallakh, Rif S.); Karippot, A (Karippot, Anoop)

Title: Chronic depression in bipolar disorder

Source: AMERICAN JOURNAL OF PSYCHIATRY, 163 (8): 1337-1341 AUG 2006

ISSN: 0002-953X

Record 93 of 183

Author(s): De los Reyes, A; Kazdin, AE

Title: Conceptualizing changes in behavior in intervention research: The range of possible changes model

Source: PSYCHOLOGICAL REVIEW, 113 (3): 554-583 JUL 2006

ISSN: 0033-295X

DOI: 10.1037/0033-295X.113.3.554

Record 94 of 183

Author(s): Skeppar, P; Adolfsson, R

Title: Bipolar II and the bipolar spectrum

Source: NORDIC JOURNAL OF PSYCHIATRY, 60 (1): 7-26 2006

ISSN: 0803-9488

Record 95 of 183

Author(s): Papakostas, GI; Petersen, TJ; Perlis, RH; Judy, AE; Burns, AM; Alpert, JE; Birnbaum, RJ; Fava, M

Title: A survey of antidepressant prescribing practices in major depression with comorbid attention-deficit hyperactivity disorder

Source: JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, 26 (2): 216-218 APR 2006

ISSN: 0271-0749

Record 96 of 183

Author(s): Moller, HJ; Grunze, H; Broich, K

Title: Do recent efficacy data on the drug treatment of acute bipolar depression support the position that drugs other than antidepressants are the treatment of choice? A conceptual review

Source: EUROPEAN ARCHIVES OF PSYCHIATRY AND CLINICAL NEUROSCIENCE, 256 (1): 1-16 FEB 2006

ISSN: 0940-1334

DOI: 10.1007/s00406-005-0591-9

Record 97 of 183

Author(s): Lin, D; Mok, H; Yatham, LN

Title: Polytherapy in bipolar disorder

Source: CNS DRUGS, 20 (1): 29-42 2006

ISSN: 1172-7047

Record 98 of 183

Author(s): Fonseca, M; Soares, JC; Hatch, JP; Santin, AP; Kapczinski, F

Title: An open trial of adjunctive escitalopram in bipolar depression

Source: JOURNAL OF CLINICAL PSYCHIATRY, 67 (1): 81-86 JAN 2006

ISSN: 0160-6689

Record 99 of 183

Author(s): Nierenberg, AA; Ostacher, MJ; Calabrese, JR; Ketter, TA; Marangell, LB; Miklowitz, DJ; Miyahara, S; Bauer, MS; Thase, ME; Wisniewski, SR; Sachs, GS

Group Author(s): STEP-BD Investigators

Title: Treatment-resistant bipolar depression: A STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone

Source: AMERICAN JOURNAL OF PSYCHIATRY, 163 (2): 210-216 FEB 2006

ISSN: 0002-953X

Record 100 of 183

Author(s): Young, RC

Title: Evidence-based pharmacological treatment of geriatric bipolar disorder

Source: PSYCHIATRIC CLINICS OF NORTH AMERICA, 28 (4): 837-+ DEC 2005

ISSN: 0193-953X

DOI: 10.1016/j.psc.2005.09.011

Back to Results

ISI Web of Knowledge
Page 1 (Articles 1 -- 100)
◄ [1 | 2] ►

Print This Page

Back to Results

ISI Web of Knowledge
Page 2 (Articles 101 -- 183)
◄ [1 | 2] ►

Print This Page

Record 101 of 183
Author(s): [Anon]
Title: Treatment of bipolar depression
Source: JOURNAL OF CLINICAL PSYCHIATRY, 66 (12): 1601-1604 DEC 2005
ISSN: 0160-6689

Record 102 of 183
Author(s): Goldberg, JF; Ghaemi, SN
Title: Benefits and limitations of antidepressants and traditional mood stabilizers for treatment of bipolar depression
Source: BIPOLAR DISORDERS, 7: 3-12 Suppl. 5 2005
ISSN: 1398-5647

Record 103 of 183
Author(s): Visser, HM; van der Mast, RC
Title: Bipolar disorder, antidepressants and induction of hypomania or mania. A systematic review
Source: WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY, 6 (4): 231-241 2005
ISSN: 1562-2975
DOI: 10.1080/15622970510029885

Record 104 of 183
Author(s): Nemeroff, CB
Title: Use of atypical antipsychotics in refractory depression and anxiety
Source: JOURNAL OF CLINICAL PSYCHIATRY, 66: 13-21 Suppl. 8 2005
ISSN: 0160-6689

Record 105 of 183
Author(s): Thase, ME
Title: Bipolar depression: Issues in diagnosis and treatment
Source: HARVARD REVIEW OF PSYCHIATRY, 13 (5): 257-271 SEP-OCT 2005
ISSN: 1067-3229
DOI: 10.1080/10673220500326425

Record 106 of 183
Author(s): Olfson, M; Das, AK; Gameroff, MJ; Pilowsky, D; Feder, A; Gross, R; Lantigua, R; Shea, S; Weissman, MM
Title: Bipolar depression in a low-income primary care clinic
Source: AMERICAN JOURNAL OF PSYCHIATRY, 162 (11): 2146-2151 NOV 2005
ISSN: 0002-953X

Record 107 of 183
Author(s): Amsterdam, JD; Shults, J
Title: Fluoxetine monotherapy of bipolar type II and bipolar NOS major depression: a double-blind, placebo-substitution, continuation study
Source: INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY, 20 (5): 257-264 SEP 2005
ISSN: 0268-1315

Record 108 of 183

Author(s): Dickstein, DP; Rich, BA; Binstock, AB; Pradella, AG; Towbin, KE; Pine, DS; Leibenluft, E

Title: Comorbid anxiety in phenotypes of pediatric bipolar disorder

Source: JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY, 15 (4): 534-548 AUG 2005

ISSN: 1044-5463

Record 109 of 183

Author(s): Ayuso-Gutiterrez, JL

Title: Depressive subtypes and efficacy of antidepressive pharmacotherapy

Source: WORLD JOURNAL OF BIOLOGICAL PSYCHIATRY, 6: 31-37 Suppl. 2 2005

ISSN: 1562-2975

DOI: 10.1080/15622970510030036

Record 110 of 183

Author(s): Yatham, LN; Kennedy, SH; O'Donovan, C; Parikh, S; MacQueen, G; McIntyre, R; Sharma, V; Silverstone, P; Alda, M; Baruch, P; Beaulieu, S; Daigneault, A; Milev, R; Young, T; Ravindran, A; Schaffer, A; Connolly, M; Gorman, CP

Title: Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines for the management of patients with bipolar disorder: consensus and controversies

Source: BIPOLAR DISORDERS, 7: 5-69 Suppl. 3 2005

ISSN: 1398-5647

Record 111 of 183

Author(s): Ghaemi, SN; Goodwin, FK

Title: Antidepressants for bipolar depression

Source: AMERICAN JOURNAL OF PSYCHIATRY, 162 (8): 1545-1546 AUG 2005

ISSN: 0002-953X

Record 112 of 183

Author(s): Hirschfeld, RMA; Fochtmann, LJ; McIntyre, JS

Title: Antidepressants for bipolar depression - To the editor

Source: AMERICAN JOURNAL OF PSYCHIATRY, 162 (8): 1546-1547 AUG 2005

ISSN: 0002-953X

Record 113 of 183

Author(s): Suppes, T; Dennehy, EB; Hirschfeld, RMA; Altshuler, LL; Bowden, CL; Calabrese, JR; Crismon, ML; Ketter, TA; Sachs, GS; Swann, AC

Group Author(s): Texas Consensus Conference Panel

Title: The Texas Implementation of Medication Algorithms: Update to the algorithms for treatment of bipolar I disorder

Source: JOURNAL OF CLINICAL PSYCHIATRY, 66 (7): 870-886 JUL 2005

ISSN: 0160-6689

Record 114 of 183

Author(s): Coryell, W

Title: Rapid cycling bipolar disorder - Clinical characteristics and treatment options

Source: CNS DRUGS, 19 (7): 557-569 2005

ISSN: 1172-7047

Record 115 of 183

Author(s): Amsterdam, JD; Shults, J

Title: Comparison of fluoxetine, olanzapine, and combined fluoxetine plus olanzapine initial therapy of bipolar type I and type II major depression - lack of manic induction

Source: JOURNAL OF AFFECTIVE DISORDERS, 87 (1): 121-130 JUL 2005

ISSN: 0165-0327

DOI: 10.1016/j.jad.2005.02.018

Record 116 of 183

Author(s): Grunze, H

Title: Reevaluating therapies for bipolar depression

Source: JOURNAL OF CLINICAL PSYCHIATRY, 66: 17-25 Suppl. 5 2005

ISSN: 0160-6689

Record 117 of 183

Author(s): Joffe, RT; MacQueen, GM; Marriott, M; Young, LT

Title: One-year outcome with antidepressant - treatment of bipolar depression

Source: ACTA PSYCHIATRICA SCANDINAVICA, 112 (2): 105-109 AUG 2005

ISSN: 0001-690X

DOI: 10.1111/j.1600-0447.2005.00583.x

Record 118 of 183

Author(s): Dubovsky, SL

Title: Treatment of bipolar depression

Source: PSYCHIATRIC CLINICS OF NORTH AMERICA, 28 (2): 349-+ JUN 2005

ISSN: 0193-953X

DOI: 10.1016/j.psc.2005.02.003

Record 119 of 183

Author(s): Post, RM

Title: Adjunctive strategies in the treatment of refractory bipolar depression: clinician options in the absence of a systematic database

Source: EXPERT OPINION ON PHARMACOTHERAPY, 6 (4): 531-546 APR 2005

ISSN: 1465-6566

DOI: 10.1517/14656566.6.4.531

Record 120 of 183

Author(s): Davis, LL; Bartolucci, A; Petty, F

Title: Divalproex in the treatment of bipolar depression: A placebo-controlled study

Source: JOURNAL OF AFFECTIVE DISORDERS, 85 (3): 259-266 APR 2005

ISSN: 0165-0327

DOI: 10.1016/j.jad.2004.09.009

Record 121 of 183

Author(s): Bowden, CL

Title: A different depression: clinical distinctions between bipolar and unipolar depression

Source: JOURNAL OF AFFECTIVE DISORDERS, 84 (2-3): 117-125 FEB 2005

ISSN: 0165-0327

DOI: 10.1016/S0165-0327(03)00194-0

Record 122 of 183
Author(s): Bowden, CL
Title: Treatment options for bipolar depression
Source: JOURNAL OF CLINICAL PSYCHIATRY, 66: 3-6 Suppl. 1 2005
ISSN: 0160-6689

Record 123 of 183
Author(s): Post, RM; Baldassano, CF; Perlis, RH; Ginsberg, DL
Title: Treatment of bipolar depression
Source: CNS SPECTRUMS, 8 (12): A1-A10 DEC 2003
ISSN: 1092-8529

Record 124 of 183
Author(s): Vo, D; Dunner, DL
Title: Treatment-resistant bipolar disorder: A comparison of rapid cyclers and nonrapid cyclers
Source: CNS SPECTRUMS, 8 (12): 948-952 DEC 2003
ISSN: 1092-8529

Record 125 of 183
Author(s): Baldassano, CF; Ballas, CA; O'Reardon, JP
Title: Rethinking the treatment paradigm for bipolar depression: The importance of long-term management
Source: CNS SPECTRUMS, 9 (9): 11-18 Suppl. 9 SEP 2004
ISSN: 1092-8529

Record 126 of 183
Author(s): Weiss, RD
Title: Treating patients with bipolar disorder and substance dependence: Lessons learned
Source: JOURNAL OF SUBSTANCE ABUSE TREATMENT, 27 (4): 307-312 DEC 2004
ISSN: 0740-5472
DOI: 10.1016/j.jsat.2004.10.001

Record 127 of 183
Author(s): Shelton, RC; Stahl, SM
Title: Risperidone and paroxetine given singly and in combination for bipolar depression
Source: JOURNAL OF CLINICAL PSYCHIATRY, 65 (12): 1715-1719 DEC 2004
ISSN: 0160-6689

Record 128 of 183
Author(s): Bowden, CL
Title: Makinig optimal use of combination pharmacotherapy in bipolar disorder
Source: JOURNAL OF CLINICAL PSYCHIATRY, 65: 21-24 Suppl. 15 2004
ISSN: 0160-6689

Record 129 of 183
Author(s): Oral, ET; Vahip, S
Title: Bipolar depression: An overview
Source: IDRUGS, 7 (9): 846-850 SEP 2004

ISSN: 1369-7056

Record 130 of 183
Author(s): Gijsman, HJ; Geddes, JR; Rendell, JM; Nolen, WA; Goodwin, GM
Title: Antidepressants for bipolar depression: A systematic review of randomized, controlled trials
Source: AMERICAN JOURNAL OF PSYCHIATRY, 161 (9): 1537-1547 SEP 2004
ISSN: 0002-953X

Record 131 of 183
Author(s): Frye, MA; Gitlin, MJ; Altshuler, LL
Title: Unmet needs in bipolar depression
Source: DEPRESSION AND ANXIETY, 19 (4): 199-208 2004
ISSN: 1091-4269
DOI: 10.1002/da.20013

Record 132 of 183
Author(s): Hahn, CG; Gyulai, L; Baldassano, CF; Lenox, RH
Title: The current understanding of lamotrigine as a mood stabilizer
Source: JOURNAL OF CLINICAL PSYCHIATRY, 65 (6): 791-804 JUN 2004
ISSN: 0160-6689

Record 133 of 183
Author(s): Bowden, CL
Title: Introduction - Managing bipolar depression
Source: JOURNAL OF CLINICAL PSYCHIATRY, 65: 3-4 Suppl. 10 2004
ISSN: 0160-6689

Record 134 of 183
Author(s): Keck, PE
Title: Evaluation and management of breakthrough depressive episodes
Source: JOURNAL OF CLINICAL PSYCHIATRY, 65: 11-15 Suppl. 10 2004
ISSN: 0160-6689

Record 135 of 183
Author(s): Belmaker, RH
Title: Medical progress: Bipolar disorder
Source: NEW ENGLAND JOURNAL OF MEDICINE, 351 (5): 476-486 JUL 29 2004
ISSN: 0028-4793

Record 136 of 183
Author(s): Young, RC; Gyulai, L; Mulsant, BH; Flint, A; Beyer, JL; Shulman, KI; Reynolds, CF
Title: Pharmacotherapy of bipolar disorder in old age - Review and recommendations\
Source: AMERICAN JOURNAL OF GERIATRIC PSYCHIATRY, 12 (4): 342-357 JUL-AUG 2004
ISSN: 1064-7481

Record 137 of 183
Author(s): Tamada, RS; Issler, CK; Amaral, JA; Sachs, GS; Lafer, B

Title: Treatment emergent affective switch: a controlled study
Source: BIPOLAR DISORDERS, 6 (4): 333-337 AUG 2004
ISSN: 1398-5647

Record 138 of 183
Author(s): Mitchell, PB
Group Author(s): Roy Au Zea Col Psy Cl Pra Bi Diso
Title: Australian and New Zealand clinical practice guidelines for the treatment of bipolar disorder
Source: AUSTRALIAN AND NEW ZEALAND JOURNAL OF PSYCHIATRY, 38 (5): 280-305 MAY 2004
ISSN: 0004-8674

Record 139 of 183
Author(s): Silverstone, PH; Sliverstone, T
Title: A review of acute treatments for bipolar depression
Source: INTERNATIONAL CLINICAL PSYCHOPHARMACOLOGY, 19 (3): 113-124 MAY 2004
ISSN: 0268-1315
DOI: 10.1091/01.yic.0000125754.83499.55

Record 140 of 183
Author(s): Ghaemi, SN; Rosenquist, KJ; Ko, JY; Baldassano, CF; Kontos, NJ; Baldessarini, RJ
Title: Antidepressant treatment in bipolar versus unipolar depression
Source: AMERICAN JOURNAL OF PSYCHIATRY, 161 (1): 163-165 JAN 2004
ISSN: 0002-953X

Record 141 of 183
Author(s): Goldberg, JF; Burdick, KE; Endick, CJ
Title: Preliminary randomized, double-blind, placebo-controlled trial of pramipexole added to mood stabilizers for treatment-resistant bipolar depression
Source: AMERICAN JOURNAL OF PSYCHIATRY, 161 (3): 564-566 MAR 2004
ISSN: 0002-953X

Record 142 of 183
Author(s): Bowden, CL; Asnis, GM; Ginsberg, LD; Bentley, B; Leadbetter, R; White, R
Title: Safety and tolerability of lamotrigine for bipolar disorder
Source: DRUG SAFETY, 27 (3): 173-184 2004
ISSN: 0114-5916

Record 143 of 183
Author(s): Post, RM; Leverich, GS; Nolen, WA; Kupka, RW; Altshuler, LL; Frye, MA; Suppes, T; McElroy, S; Keck, P; Grunze, H; Walden, J
Title: A re-evaluation of the role of antidepressants in the treatment of bipolar depression: data from the Stanley Foundation Bipolar Network
Source: BIPOLAR DISORDERS, 5 (6): 396-406 DEC 2003
ISSN: 1398-5647

Record 144 of 183
Author(s): Goldberg, JF; Truman, CJ
Title: Antidepressant-induced mania: an overview of current controversies

Source: BIPOLAR DISORDERS, 5 (6): 407-420 DEC 2003
ISSN: 1398-5647

Record 145 of 183
Author(s): Ghaemi, SN; Hsu, DJ; Soldani, F; Goodwin, FK
Title: Antidepressants in bipolar disorder: the case for caution
Source: BIPOLAR DISORDERS, 5 (6): 421-433 DEC 2003
ISSN: 1398-5647

Record 146 of 183
Author(s): Dunner, DL
Title: Clinical consequences of under-recognized bipolar spectrum disorder
Source: BIPOLAR DISORDERS, 5 (6): 456-463 DEC 2003
ISSN: 1398-5647

Record 147 of 183
Author(s): Sanderson, K; Andrews, G; Corry, J; Lapsley, H
Title: Reducing the burden of affective disorders: is evidence-based health care affordable?
Source: JOURNAL OF AFFECTIVE DISORDERS, 77 (2): 109-125 NOV 2003
ISSN: 0165-0327
DOI: 10.1016/S0165-0327(03)00134-4

Record 148 of 183
Author(s): Muzina, DJ; Calabrese, JR
Title: Recent placebo-controlled acute trials in bipolar depression: focus on methodology
Source: INTERNATIONAL JOURNAL OF NEUROPSYCHOPHARMACOLOGY, 6 (3): 285-291 SEP 2003
ISSN: 1461-1457
DOI: 10.1017/S1461145703003559

Record 149 of 183
Author(s): Kasper, S
Title: Issues in the treatment of bipolar disorder
Source: EUROPEAN NEUROPSYCHOPHARMACOLOGY, 13: S37-S42 Suppl. 2 AUG 2003
ISSN: 0924-977X
DOI: 10.1016/S0924-977X(03)00076-2

Record 150 of 183
Author(s): Goodwin, FK; Fireman, B; Simon, GE; Hunkeler, EM; Lee, J; Revicki, D
Title: Suicide risk in bipolar disorder during treatment with lithium and divalproex
Source: JAMA-JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, 290 (11): 1467-1473 SEP 17 2003
ISSN: 0098-7484

Record 151 of 183
Author(s): Coryell, W; Solomon, D; Turvey, C; Keller, M; Leon, AC; Endicott, J; Schettler, P; Judd, L; Mueller, T
Title: The long-term course of rapid-cycling bipolar disorder
Source: ARCHIVES OF GENERAL PSYCHIATRY, 60 (9): 914-920 SEP 2003
ISSN: 0003-990X

Record 152 of 183

Author(s): Sachs, GS

Title: Decision tree for the treatment of bipolar disorder

Source: JOURNAL OF CLINICAL PSYCHIATRY, 64: 35-40 Suppl. 8 2003

ISSN: 0160-6689

Record 153 of 183

Author(s): Ricci, E; Parazzini, F; Mirone, V; Imbimbo, C; Palmieri, A; Bortolotti, A; Di Cintio, E; Landoni, M; Lavezzari, M

Title: Current drug use as risk factor for erectile dysfunction: results from an Italian epidemiological study

Source: INTERNATIONAL JOURNAL OF IMPOTENCE RESEARCH, 15 (3): 221-224 JUN 2003

ISSN: 0955-9930

DOI: 10.1038/sj.ijir.3901008

Record 154 of 183

Author(s): Shelton, RC

Title: The combination of olanzapine and fluoxetine in mood disorders

Source: EXPERT OPINION ON PHARMACOTHERAPY, 4 (7): 1175-1183 JUL 2003

ISSN: 1465-6566

Record 155 of 183

Author(s): Altshuler, L; Suppes, T; Black, D; Nolen, WA; Keck, PE; Frye, MA; McElroy, S; Kupka, R; Grunze, H; Walden, J; Leverich, G; Denicoff, K; Luckenbaugh, D; Post, R

Title: Impact of antidepressant discontinuation after acute bipolar depression remission on rates of depressive relapse at 1-year follow-up

Source: AMERICAN JOURNAL OF PSYCHIATRY, 160 (7): 1252-1262 JUL 2003

ISSN: 0002-953X

Record 156 of 183

Author(s): DelBello, MP; Carlson, GA; Tohen, M; Bromet, EJ; Schwiers, M; Strakowski, SM

Title: Rates and predictors of developing a manic or hypomanic episode 1 to 2 years following a first hospitalization for major depression with psychotic features

Source: JOURNAL OF CHILD AND ADOLESCENT PSYCHOPHARMACOLOGY, 13 (2): 173-185 SUM 2003

ISSN: 1044-5463

Record 157 of 183

Author(s): Zarate, CA; Quiroz, JA

Title: Combination treatment in bipolar disorder: a review of controlled trials

Source: BIPOLAR DISORDERS, 5 (3): 217-225 JUN 2003

ISSN: 1398-5647

Record 158 of 183

Author(s): Thase, ME; Bhargava, M; Sachs, GS

Title: Treatment of bipolar depression: current status, continued challenges, and the STEP-BD approach

Source: PSYCHIATRIC CLINICS OF NORTH AMERICA, 26 (2): 495-+ JUN 2003

ISSN: 0193-953X

DOI: 10.1016/S0193-953X(03)00029-7

Record 159 of 183

Author(s): Keck, PE; Nelson, EB; McElroy, SL
Title: Advances in the Pharmacologic treatment of bipolar depression
Source: BIOLOGICAL PSYCHIATRY, 53 (8): 671-679 APR 15 2003
ISSN: 0006-3223
DOI: 10.1016/S0006-3223(03)01741-9

Record 160 of 183
Author(s): Altshuler, LL; Frye, MA; Gitlin, MJ
Title: Acceleration and augmentation strategies for treating bipolar depression
Source: BIOLOGICAL PSYCHIATRY, 53 (8): 691-700 APR 15 2003
ISSN: 0006-3223
DOI: 10.1016/S0006-3223(03)00087-8

Record 161 of 183
Author(s): Yatham, LN; Calabrese, JR; Kusumakar, V
Title: Bipolar depression: criteria for treatment selection, definition of refractoriness, and treatment options
Source: BIPOLAR DISORDERS, 5 (2): 85-97 APR 2003
ISSN: 1398-5647

Record 162 of 183
Author(s): Ernst, CL; Goldberg, JF
Title: Antidepressant properties of anticonvulsant drugs for bipolar disorder
Source: JOURNAL OF CLINICAL PSYCHOPHARMACOLOGY, 23 (2): 182-192 APR 2003
ISSN: 0271-0749

Record 163 of 183
Author(s): Keck, PE; McElroy, SL
Title: New approaches in managing bipolar depression
Source: JOURNAL OF CLINICAL PSYCHIATRY, 64: 13-18 Suppl. 1 2003
ISSN: 0160-6689

Record 164 of 183
Author(s): Khan, A; Khan, S
Title: Placebo in mood disorders: the tail that wags the dog
Source: CURRENT OPINION IN PSYCHIATRY, 16 (1): 35-39 JAN 2003
ISSN: 0951-7367
DOI: 10.1097/01.yco.0000049397.00317.ac

Record 165 of 183
Author(s): Thase, ME; Sachs, GS
Title: The challenges of pharmacotherapy of bipolar depression
Source: CLINICAL NEUROSCIENCE RESEARCH, 2 (3-4): 213-221 DEC 2002
ISSN: 1566-2772

Record 166 of 183
Author(s): Bhagwagar, Z; Goodwin, GA
Title: The role of lithium in the treatment of bipolar depression

Source: CLINICAL NEUROSCIENCE RESEARCH, 2 (3-4): 222-227 DEC 2002
ISSN: 1566-2772

Record 167 of 183
Author(s): Malhi, GS; Mitchell, PB; Salim, S
Title: Bipolar depression - Management options
Source: CNS DRUGS, 17 (1): 9-25 2003
ISSN: 1172-7047

Record 168 of 183
Author(s): Frankle, WG; Perlis, RH; Deckersbach, T; Grandin, LD; Gray, SM; Sachs, GS; Nierenberg, AA
Title: Bipolar depression: relationship between episode length and antidepressant treatment
Source: PSYCHOLOGICAL MEDICINE, 32 (8): 1417-1423 NOV 2002
ISSN: 0033-2917
DOI: 10.1017/S0033291702006165

Record 169 of 183
Author(s): Hollon, SD; Thase, ME; Markowitz, JC
Title: Treatment and prevention of depression
Source: PSYCHOLOGICAL SCIENCE: 39-77 Suppl. S NOV 2002
ISSN: 0956-7976

Record 170 of 183
Author(s): Baldessarini, RJ
Title: Treatment research in bipolar disorder - Issues and recommendations
Source: CNS DRUGS, 16 (11): 721-729 2002
ISSN: 1172-7047

Record 171 of 183
Author(s): Calabrese, JR; Shelton, MD; Rapport, DJ; Kimmel, SE; Elhaj, O
Title: Long-term treatment of bipolar disorder with lamotrigine
Source: JOURNAL OF CLINICAL PSYCHIATRY, 63: 18-22 Suppl. 10 2002
ISSN: 0160-6689

Record 172 of 183
Author(s): Fagiolini, A; Frank, E; Cherry, CR; Houck, PR; Novick, DM; Buysse, DJ; Kupfer, DJ
Title: Clinical indicators for the use of antidepressants in the treatment of bipolar I depression
Source: BIPOLAR DISORDERS, 4 (5): 277-282 OCT 2002
ISSN: 1398-5647

Record 173 of 183
Author(s): Jain, V; Swartz, CM
Title: Charcoal enhancement of treatment for tricyclic-induced mania
Source: PHARMACOPSYCHIATRY, 35 (5): 197-199 SEP 2002
ISSN: 0176-3679

Record 174 of 183

Author(s): Haddad, P; Dursun, S

Title: Pharmacological management of bipolar depression

Source: ACTA PSYCHIATRICA SCANDINAVICA, 105 (6): 401-403 JUN 2002

ISSN: 0001-690X

Record 175 of 183

Author(s): Vieta, E; Martinez-Aran, A; Goikolea, JM; Torrent, C; Colom, F; Benabarre, A; Reinares, M

Title: A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers

Source: JOURNAL OF CLINICAL PSYCHIATRY, 63 (6): 508-512 JUN 2002

ISSN: 0160-6689

Record 176 of 183

Author(s): McIntyre, RS; Mancini, DA; McCann, S; Srinivasan, J; Sagman, D; Kennedy, SH

Title: Topiramate versus Bupropion SR when added to mood stabilizer therapy for the depressive phase of bipolar disorder: a preliminary single-blind study

Source: BIPOLAR DISORDERS, 4 (3): 207-213 JUN 2002

ISSN: 1398-5647

Record 177 of 183

Author(s): El-Mallakh, RS; Karippot, A

Title: Use of antidepressants to treat depression in bipolar disorder

Source: PSYCHIATRIC SERVICES, 53 (5): 580-584 MAY 2002

ISSN: 1075-2730

Record 178 of 183

Author(s): Suppes, T; Dennehy, EB; Swann, AC; Bowden, CL; Calabrese, JR; Hirschfeld, RMA; Keck, PE; Sachs, GS; Crismon, ML; Toprac, MG; Shon, SR

Group Author(s): Texas Consensus Conf Panel Med Tr

Title: Report of the Texas Consensus Conference Panel on Medication Treatment of Bipolar Disorder 2000

Source: JOURNAL OF CLINICAL PSYCHIATRY, 63 (4): 288-299 APR 2002

ISSN: 0160-6689

Record 179 of 183

Author(s): [Anon]

Title: Practice guideline for the treatment of patients with bipolar disorder (revision) - Introduction

Source: AMERICAN JOURNAL OF PSYCHIATRY, 159 (4): 2-50 Suppl. S APR 2002

ISSN: 0002-953X

Record 180 of 183

Author(s): Rivas-Vazquez, RA; Johnson, SL; Rey, GJ; Blais, MA; Rivas-Vazquez, A

Title: Current treatments for bipolar disorder: A review and update for psychologists

Source: PROFESSIONAL PSYCHOLOGY-RESEARCH AND PRACTICE, 33 (2): 212-223 APR 2002

ISSN: 0735-7028

DOI: 10.1037//0735-7028.33.2.212

Record 181 of 183

Author(s): Charney, DS; Nemeroff, CB; Lewis, L; Laden, SK; Gorman, JM; Laska, EM; Borenstein, M; Bowden, CL; Caplan, A; Emslie, GJ; Evans, DL; Geller, B; Grabowski, LE; Herson, J; Kalin, NH; Keck, PE; Kirsch, I; Krishnan, KRR; Kupfer, DJ; Makuch, RW; Miller, FG; Pardes, H; Post, R; Reynolds, MM; Roberts, L; Rosenbaum, JF; Rosenstein, DL; Rubinow, DR; Rush, AJ; Ryan, ND; Sachs, GS; Schatzberg, AF; Solomon, S

Group Author(s): Consensus Dev Panel

Title: National depressive and manic-depressive association consensus statement on the use of placebo in clinical trials of mood disorders

Source: ARCHIVES OF GENERAL PSYCHIATRY, 59 (3): 262-270 MAR 2002

ISSN: 0003-990X

Record 182 of 183

Author(s): Ketter, TA; Calabrese, JR

Title: Stabilization of mood from below versus above baseline in bipolar disorder: A new nomenclature

Source: JOURNAL OF CLINICAL PSYCHIATRY, 63 (2): 146-151 FEB 2002

ISSN: 0160-6689

Record 183 of 183

Author(s): Muller-Oerlinghausen, B; Berghofer, A; Bauer, M

Title: Bipolar disorder

Source: LANCET, 359 (9302): 241-247 JAN 19 2002

ISSN: 0140-6736

Back to Results

ISI Web of Knowledge
Page 2 (Articles 101 -- 183)
◄ [1 | 2] ►

Print This Page

Attachment D

639

MD pts on Li coming into study. Some + valproate etc — were these continued?

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A Double-Blind, Placebo-Controlled Comparison of Imipramine and Paroxetine in the Treatment of Bipolar Depression

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ABSTRACT

Objective: This study compared the efficacy and safety of paroxetine and imipramine with placebo for bipolar depression in adult outpatients stabilized on lithium. Method: In a double-blind, placebo-controlled study, 117 outpatients with DSM-III-R bipolar disorder, depressive phase, were randomized to paroxetine (n=35), imipramine (n=39), or placebo (n=43) for 10 weeks. In addition to monotherapy with lithium, patients may have received either carbamazepine or valproate combined with lithium for control of manic symptoms. Patients were stratified by high- (>0.8 mEq/L) and low- (≤0.8 mEq/L) trough serum lithium levels determined at the screening visit. Primary efficacy was assessed by change from baseline Hamilton Rating Scale for Depression (HAMD) and Clinical Global Impressions (CGI) severity of illness scales. Results: Differences in overall efficacy between the 3 groups were not statistically significant. The end point antidepressant response in patients with high serum lithium levels also did not separate significantly from placebo. However, both paroxetine and imipramine were superior to placebo in patients with low serum lithium levels. Compared with imipramine, paroxetine resulted in a lower incidence of adverse events, most notably emergence of manic symptoms. Conclusions: Antidepressants may not be useful adjunctive therapy in patients with bipolar depression with high serum lithium levels. However,

antidepressant therapy may be beneficial for patients who cannot tolerate high serum lithium levels or who are refractory to the antidepressant effects of lithium.

INTRODUCTION

The treatment of bipolar depression represents a clinical challenge, and appropriate treatment strategies remain more anecdotal than data-based. In contrast to the extensive literature guiding treatment of patients with unipolar depression, treatment of bipolar depression has not been extensively studied and effective treatments are not well-defined (1,2). Lithium is considered standard mood-stabilizing therapy for bipolar disorder (3-6). However, up to 50% of patients effectively maintained on lithium therapy may be unresponsive to its antidepressant effects (4,7). When lithium monotherapy is not effective in managing depression or if patients are unable to tolerate the side effects of high lithium serum levels, patients with bipolar disorder may require combination therapy with antidepressants (3).

Monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), bupropion, and the selective serotonin reuptake inhibitors (SSRIs) have been evaluated for treatment of the depressive component of bipolar disorder (2,3,6,8,9). In a comparison of imipramine and tranylcypromine in depressed patients with bipolar disorder, the response rate (defined as an end point Clinical Global Impressions (CGI) score of ≥2 or 3) to imipramine was 48% and the response rate for tranylcypromine was

greater than 80% (10). However, Prien et al. (11) noted that combined imipramine/lithium therapy offered no advantage over lithium alone in the treatment of bipolar depression. Additional clinical trials have demonstrated that the TCAs have a response rate (defined as ≥50% improvement in baseline Hamilton Rating Scale for Depression [HAMD] total score) between 50% and 70% in the treatment of bipolar depression (10,12-14). Bupropion was as effective as desipramine in one double-blind comparative study (14). Only a limited number of trials have evaluated the effectiveness of SSRIs in the treatment of bipolar depression (13,15,16). Cohn et al. (13) reported that bipolar patients treated with fluoxetine had a significantly greater response rate than those treated with imipramine. In a 6-week, double-blind comparison of paroxetine and amitriptyline in lithium-stabilized patients with breakthrough major depression, Bauer et al. (15) reported significantly greater responses on the HAMD and CGI severity of illness scores in paroxetine-treated patients.

Although the MAOIs appear to be effective in treating bipolar depression, safety issues and dietary restrictions often limit their use in general clinical practice. Therapy with TCAs is also associated with a high incidence of adverse events, and many patients are unable to tolerate the anticholinergic side effects (13). Both TCAs and MAOIs have a low therapeutic index, which is a major concern in patients with bipolar disorder because of

their high rate of suicide attempts. The SSRIs have a lower incidence of adverse events, particularly anticholinergic and cardiac effects (17,18). Thus, the safety profile of SSRIs may offer an advantage over TCAs and MAOIs and may increase patient compliance.

The potential for the so-called "switch" into mania is another risk that must be considered when initiating antidepressant therapy in patients with bipolar depression (19-22). In one analysis, induction of mania occurred in 3.7% of 242 bipolar patients treated with SSRIs and in 11.2% of 125 patients treated with TCAs (20). Bupropion has been reported to induce mania in one small, open-label series (23). However, other investigators have reported that, when added to lithium, thyroxine, or anticonvulsant regimens, bupropion is not associated with mania in rapidly cycling patients (24) and is less likely to induce mania than desipramine (14).

In order to address some of the unresolved issues regarding the treatment of bipolar depression, we compared the efficacy and safety of paroxetine and imipramine with that of placebo in the treatment of bipolar depression in adult outpatients stabilized on lithium therapy.

METHOD

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled study that was conducted to assess the efficacy and safety of paroxetine and imipramine in combination with lithium therapy in the treatment of bipolar depression. Outpatients diagnosed with bipolar disorder currently in a major depressive episode were enrolled. A 1-week, single-blind, placebo period was used to screen potential patients for inclusion in the study.

Diagnostic procedures included DSM-III-R multiaxial evaluation, psychiatric and medical histories, electrocardiogram (ECG), pregnancy test, vital signs, physical examination, serum trough lithium level, body weight, routine laboratory analyses, and administration of the 21-item version of the HAMD (25) and the CGI severity of illness scales. Following psychiatric and medical screening, eligible patients were stratified into 2 groups based on lithium trough serum level at the screening visit (≤0.8 mEq/L and >0.8 mEq/L), and at baseline were randomly assigned to 1 of the 3 treatment groups.

Patients randomized to paroxetine received 20 mg daily for the first 3 weeks; thereafter, dosage increases of 10 mg/d were permitted every 7 days based on therapeutic response up to a

maximum dose of 50 mg/d. Patients receiving imipramine began at a dose of 50 mg/d with a forced titration to 150 mg/d at the rate of 50 mg every 7 days over the first 3 weeks of the study. After the titration period for patients receiving imipramine, dosage increases of 50 mg/d were permitted every 7 days based on therapeutic response up to a maximum dose of 300 mg/d. Dosage reduction was permitted once if necessary for adverse events; re-titration to the original dose level was allowed if the adverse event remitted. Following the 10-week treatment phase, patients were gradually tapered off all study medications.

The study was approved by the institutional review board at each of the 19 participating centers, and each patient provided written informed consent prior to entry into the study.

Patient Selection

All patients enrolled in the study fulfilled DSM-III-R criteria for bipolar disorder and scored ≥15 on the 21-item version of the HAMD at both the screen and baseline evaluations. The total HAMD score could not decrease by more than 25% between the screen and baseline evaluations. Eligible patients experienced at least one previous episode of mania or major depression within the past 5 years, were maintained on lithium monotherapy or a combination of lithium/sodium valproate or lithium/carbamazapine for at least 7 weeks prior to the screen visit, and maintained serum lithium

levels between 0.5 and 1.2 mEq/L (0.4 mEq/L in patients intolerant to lithium) for at least 6 weeks prior to the screening evaluation. Serum lithium concentrations were measured 1 week after initiation of study medication and were within prior defined levels for all eligible patients. Lithium dosage adjustments were not allowed unless serum levels deviated beyond the 0.5 to 1.2 mEq/L range (0.4 mEq/L for lithium intolerance), in which case doses were adjusted to maintain levels within the permitted range. Patients were at least 18 years old.

Patients who met DSM-III-R criteria for bipolar disorder but who were not currently depressed were excluded, as were patients who required therapy with both sodium valproate and carbamazapine or those who had been diagnosed with Axis I disorders other than bipolar disorder as the primary disorder within 6 months prior to screening, including dysthymia and bipolar II disorder. Patients who were rapid cyclers (≥4 manic/hypomanic or depressive episodes within 12 months prior to baseline), who had recent manic/hypomanic episodes (within 4 weeks of baseline), and who were prone to spontaneous remission (depressive episodes of ≤8 weeks' duration) were excluded. Also among the exclusion criteria were any serious medical disorder or condition, such as cardiovascular disease or history of narrow-angle glaucoma, that would preclude the administration of TCA therapy; concomitant therapy with other psychotropic drugs, not including chloral

hydrate; and concomitant therapy with warfarin, cardiac glycosides, phenytoin, cimetidine, type 1C antiarrhythmic agents, quinidine, sulfonylurea derivatives, or tryptophan. Patients who met the DSM-III-R criteria for substance abuse within 3 months prior to the study or the criteria for substance dependence within 6 months prior to the study were ineligible. Patients who were judged by the investigator to be at serious suicidal or homicidal risk were also excluded from the study.

Assessment

During the 10-week study period, patients were assessed for both efficacy and adverse events at baseline and at weeks 1, 2, 3, 4, 5, 6, 8, and 10. Laboratory evaluations and ECG were conducted at the screening visit and at weeks 4 and 10. Baseline laboratory evaluations were only performed if abnormal values were noted at the screening visit.

Primary efficacy parameters were mean change from baseline in the total score of the first 17 items of the HAMD and mean change from baseline in the CGI severity of illness item. Clinical response parameters included the proportion of patients achieving HAMD scores ≤7 and the proportion of patients with CGI global improvement scores ≤2. These parameters are clinically accepted as indicative of therapeutic response.

Safety evaluations were based on routine adverse-event monitoring, vital sign assessments, and a hypomania/mania assessment based on DSM-III-R criteria. Patients were asked a nonleading question at each post-baseline assessment, such as "Do you feel differently in any way since starting this treatment?" Positive responses were investigated and documented on the case report form. These evaluations, as well as body weight determinations, were evaluated at each visit. The effect of paroxetine and imipramine on serum lithium concentrations was monitored by obtaining blood samples at weeks 2, 4, 6, and 10. Adverse events were elicited by asking the patient nonleading questions.

Data Analysis

Data are presented from the intent-to-treat population. The end point dataset was the primary timepoint of interest and was determined based on the last available on-therapy observation for each patient. Patients were stratified into high- (>.8 mEq/L) or low- (≤.8 mEq/L) serum lithium concentration groups based on screening visit serum lithium levels. Lithium stratification criteria were determined a priori. The proportion of patients achieving dichotomous response was analyzed by the Cochran-Mantel-Haenszel test adjusting for lithium stratification or by Fisher's exact test. The Chi-square test was used for analyses within lithium strata. Change from baseline score, defined as

score minus baseline score, of efficacy scales was assessed by parametric analysis-of-variance methodology. The study was designed to enroll 35 patients per arm, which would allow 70% power to detect a 5-point difference on the HAMD score (SD=0.5) between treatment groups.

The primary comparison of interest was between the paroxetine and placebo treatment groups regardless of lithium stratification. Because all other statistical comparisons were considered to be secondary, no adjustments for multiple comparisons were made. Therefore, the achievement of statistical significance for the primary efficacy variables at end point (eg, HAMD change from baseline and CGI severity of illness change from baseline) is $p \leq 0.05$.

The general linear model (GLM) procedure of the Statistical Analysis System (SAS) was used to perform the analysis with a model that included effects for treatment and lithium strata for HAMD total (first 17 items) and CGI severity of illness. Analyses of all other efficacy variables were performed with a model that included only an effect for treatment. Additional analyses were performed within lithium strata that included only the treatment effect. Type III sums of squares were used. The analyses were designed to include an effect for the investigator, however, 14 of the 19 investigational sites had fewer than 8 total patients. Thus, no analyses were performed using an

investigator effect. The treatment-by-lithium strata interaction was found to be nonsignificant and was not included in the model. Because only a small number of patients experienced manic and hypomanic episodes, these episodes were not analyzed.

All statistical tests were two-tailed. Tests of hypothesis of interactions were made at the 10% significance level, and all other tests were made at the 5% significance level. Data are presented as means and standard deviations. The CONTRAST statement from the GLM procedure of SAS was used for treatment group comparisons. Interaction assessments were conducted as per protocol. However, significant interactions were not found and therefore not presented.

RESULTS

Demographic and Clinical Characteristics

A total of 117 outpatients were enrolled by 19 centers: 35 patients were randomly assigned to the paroxetine group, 39 to the imipramine group, and 43 to the placebo group. The groups were similar in the distributions of age, gender, race (table 1), and cardiac history. Concomitant medications were used by 82.9% of patients in the paroxetine treatment group, 76.9% of patients in the imipramine group, and 81.4% of patients in the placebo group. The concomitant use of valproic acid was similar for the

paroxetine (11.4%) and placebo (9.3%) groups and much less for imipramine (2.6%); only 1 patient in the paroxetine (2.9%) and imipramine (2.6%) groups received carbamazepine during the study. Because of the small number of patients receiving concomitant therapy with these agents, no influence on overall efficacy in the treatment groups could be determined.

Mean daily doses at study end point (i.e., the last available on-therapy observation for each patient) were 32.6 mg for paroxetine (range: 20 to 50 mg) and 166.7 mg for imipramine (range: 50 to 300 mg). At end point, 5 patients were receiving daily doses of imipramine lower than the 150-mg minimum daily dosage required by the protocol (2 patients: 50 mg; 3 patients: 100 mg).

Efficacy

The mean change from baseline at end point on the HAMD and CGI severity of illness scales in the paroxetine and imipramine total response dataset was not significantly different than the placebo-treated group (table 2). A high placebo response rate also occurred in the high-serum lithium level group, with no statistical separation from placebo for either paroxetine or imipramine. However, in patients stratified to the low-serum lithium level group, paroxetine and imipramine were superior to

placebo for mean change from baseline on the HAMD and CGI severity of illness scale scores (table 2).

Therapeutic response was defined as HAMD ≤7 or CGI ≤2. There were no statistically significant differences between paroxetine, imipramine, or placebo among the total intent-to-treat population for the HAMD ≤7 end point criterion (paroxetine, N=15 [45.5%]; imipramine, N=14 [38.9%]; placebo, N=15 [34.9%]) or end point CGI ≤2 (paroxetine, N=18 [54.5%]; imipramine, N=21 [58.3%]; placebo, N=20 [46.5%]). Among the study completers, 56% of 25 paroxetine-treated patients, 47.8% of 23 imipramine-treated patients, and 53.8% of 26 placebo patients responded to treatment with a HAMD score of ≤7. Similarly, 68% of paroxetine patients in the total response dataset, 73.9% of imipramine patients, and 69.2% of placebo patients responded to treatment with a CGI score of ≤2.

Similar end point responses were noted in patients stratified to the high-serum lithium level group in the HAMD response (paroxetine, N=5 [35.7%]; imipramine, N=7 [41.2%]; placebo, N=8 [38.1%]) and the CGI response (paroxetine, N=8 [57.1%]; imipramine, N=8 [47.1%]; placebo, N=11 [52.4%]). In the low-serum lithium level group, there was no between-group statistical separation using the HAMD response criterion (paroxetine, N=10 [52.6%]; imipramine, N=7 [36.8%]; placebo, N=7

[31.8%]) or the CGI response criterion (paroxetine, N=10 [52.6%]; imipramine, N=13 [68.4%]; placebo, N=9 [40.9%]).

There were 5 patients in the imipramine group who did not reach the 150-mg dose at end point. Each of these patients (2 at 50-mg and 3 at 100-mg) withdrew from the study prior to reaching the 150-mg dose level at week 3. The duration of therapy in these patients ranged from 5 to 14 days. In 4 patients (1 from the 50-mg group and 3 from the 100-mg group), the HAMD decreased 1 to 18 points; in 1 patient, the HAMD increased 2 points.

Emergent Adverse Events

Treatment-emergent adverse events were determined by asking open-ended, nonleading questions. Tremor (40%), insomnia (37.1%), and somnolence (34.3%) were the most frequently reported effects in the paroxetine-treated patients. For the patients in the imipramine group, dry mouth (61.5%), tremor (38.5%), and headache (41.0%) were noted most commonly. In the placebo group, headache (39.5%), somnolence (25.6%), and insomnia (23.3%) were the most frequently occurring adverse events, with tremor occurring in 9.3% of patients. Patients treated with imipramine reported a higher incidence of abnormal ejaculation and impotence (18.8% and 25.0%, respectively) compared with patients receiving paroxetine (0.0% and 6.3%, respectively) or placebo (5.0% and 0.0%, respectively).

Adverse events precipitated study discontinuation in 1 paroxetine patient (2.9%), 12 imipramine patients (30.8%), and 5 placebo patients (11.6%). Other reasons for withdrawal from the study included lack of efficacy (paroxetine, 2.9%; imipramine, 2.6%; placebo, 18.6%), deviation from protocol (including noncompliance) (paroxetine, 5.7%; imipramine, 5.1%; placebo, 2.3%), and subjects lost to follow-up (paroxetine, 17.1%; imipramine, 2.6%; placebo, 4.7%).

No serious adverse events were reported in the paroxetine group. Two patients in the imipramine group (5%) and 4 patients in the placebo group (9%) experienced serious adverse events. In the imipramine group, 1 patient was hospitalized for mania on study day 42 and another patient developed physical aggression with homicidal ideation and was withdrawn from the study on day 29. Of the 4 placebo-treated patients experiencing serious adverse events, 2 were hospitalized for manic episodes (not necessarily protocol-defined mania), 1 developed increased depression with paranoid hallucinations and delusions, and the fourth did not complete the taper phase and developed reemergence of depression. The adverse events associated with active treatment were consistent with the safety profiles for SSRIs and TCAs.

By definition, participating patients did not meet the DSM-III-R criteria for hypomania or mania at screen or baseline. End point analysis revealed that no paroxetine-treated patients experienced induction to mania in any of the stratification groups or in the total patient population. However, 3 patients (8.3%) treated with imipramine and 1 patient (2.3%) treated with placebo in the total population experienced treatment-emergent mania. In the lithium strata, the incidence of mania was 5.9% and 10.5% in the high- and low-lithium level groups, respectively, for the patients treated with imipramine. One placebo-treated patient (4.5%) in the low-serum lithium level group developed mania. None of the placebo-treated patients in the high-serum lithium level group experienced treatment-emergent mania.

Lithium concentrations remained within the therapeutic range for all patients treated with paroxetine or imipramine (figure). There was no evidence that either paroxetine or imipramine influenced lithium pharmacokinetics. Weight gain was observed in 3 patients (7.7%) treated with imipramine and in 3 patients (7.0%) in the placebo group. Four patients treated with paroxetine experienced a change in weight: 2 (5.7%) gained weight, and 2 (5.7%) lost weight.

DISCUSSION

This is the largest study evaluating an SSRI for the treatment of bipolar depression and the first controlled clinical trial assessing the efficacy and safety of paroxetine in this disorder. In both the total population and the high-lithium stratification groups, neither paroxetine nor imipramine separated from placebo. However, in the end point analysis, patients with low serum lithium levels who were treated with paroxetine or imipramine demonstrated significant improvement compared with placebo.

Although our study was not designed to measure the antidepressant effects of lithium, when lithium stratification groups are compared, it could be inferred from the data that the antidepressant effects of lithium are more prominent in patients with high serum lithium levels. The antidepressant effects of high serum lithium levels are not surprising in view of the considerable literature suggesting an antidepressant effect of lithium in bipolar depression and to a lesser extent in unipolar depression and depression associated with schizoaffective disorder (6,26-28).

Clinical response parameters were HAMD ≤7 or CGI global improvement ≤2 for the end point analysis and the completer analysis. Overall, in the clinical response analyses, we

observed no statistically significant differences between the treatment groups. The lack of statistical difference between treatment groups in these analyses may be associated with the relatively small patient population and the high placebo response rate in the lithium-treated patients. Tondo et al. (29) reported in an open study of 26 patients with bipolar disorder that fluoxetine was effective in treating depressive episodes. Interestingly, the mean serum lithium level in these patients was 0.57 mEq/L, well within our low-serum lithium level group.

Paroxetine was well-tolerated in these patients. Adverse events led to withdrawal from the study for 1 patient (3%) in the paroxetine group compared with 12 patients (31%) in the imipramine group. These findings are consistent with other reports of adverse events during SSRI therapy (12,17,30).

Resting tremor was noted by 40.0%, 38.5%, and 9.3% of patients treated with paroxetine, imipramine, and placebo, respectively. Psychopharmacologically active drugs, including TCAs and SSRIs, may exacerbate existing lithium-related tremor (15,31,32). Although baseline tremor was not assessed making it impossible to determine the causal relationship of paroxetine or imipramine, tremor was likely associated with lithium, inasmuch as similar rates of tremor have been reported in patients with bipolar disorder maintained on lithium alone (31-33). The high incidence

of anticholinergic adverse reactions and tremor has also been reported in previous studies evaluating imipramine alone and imipramine and lithium combination therapy (11,12).

Imipramine-treated patients voluntarily reported a higher incidence of abnormal ejaculation (18.8%) and impotence (25%) compared with paroxetine-treated patients. In clinical trials evaluating paroxetine in unipolar depression, sexual dysfunction was reported in 6% to 33% of patients (34,35). In our study, the incidence of abnormal ejaculation and impotence was 0% and 6.3%, respectively, in paroxetine-treated patients.

There is considerable evidence supporting the association of antidepressants and the induction of mania and rapid cycling in patients with bipolar disorder (19-22,36). Paroxetine did not precipitate a switch to mania in any lithium stratification group or in the overall study population, whereas the incidence of mania in imipramine-treated patients was 5.9% and 10.5% in the high- and low-lithium level groups, respectively. In the analysis of the total population, 8.3% of patients receiving imipramine and 2.3% of patients in the placebo group developed mania. It should be noted, however, that concomitant use of valproic acid was more common in the paroxetine (11.4%) and placebo (9.3%) groups than in the imipramine group (2.6%). This is consistent with previous studies that also have shown a high

propensity for imipramine to cause mania (10,11,37). In a review of other similar clinical trials, TCAs (11.2%) were much more likely to induce a switch to mania in patients with bipolar depression than were SSRIs (3.7%; $p<0.01$ vs TCAs) or placebo (4.2%) (20).

In evaluating the effect of paroxetine and imipramine on serum lithium levels, lithium concentrations remained within the accepted therapeutic range throughout the course of the study. No treatment-emergent adverse events were attributed to lithium toxicity. These results are consistent with previous studies that evaluated the effects of concomitant imipramine (11,37) and paroxetine (38) on lithium levels in patients with bipolar disorder. Thus, the lack of effect by paroxetine and imipramine on lithium toxicity minimizes additional safety concerns regarding the use of lithium with these agents.

Several limitations of our study must be considered. The high response rate in the placebo group and the small sample sizes may have limited our ability to detect statistical differences between treatment groups. All patients in the paroxetine group were on therapeutic daily doses of paroxetine (20 to 50 mg), but 5 patients in the imipramine group (13.9%) were receiving daily doses of 50 mg or 100 mg, which are at the lower end of the therapeutic range for this antidepressant. Previous studies

indicate that as many as one half of patients receiving lithium may respond to the antidepressant effects of this agent (4,7). Furthermore, carbamazepine may be useful in the treatment of refractory depression (39). Thus, all patients in this study were receiving medication (i.e., lithium and, in a small number of patients, carbamazepine or valproate) capable of improving scores on the depression efficacy scales. It is unlikely that the low rate of concomitant carbamazepine or valproate use in this study influenced overall outcome. However, it is noteworthy that an antidepressant effect was evident in patients in the total patient population analysis, as well as in the high-lithium level group. Yet in those patients receiving active drug and maintained on low lithium serum levels, a pronounced therapeutic effect was demonstrated with imipramine and paroxetine, and statistical separation from placebo was achieved.

The results of this study indicate that patients with bipolar depression who maintain high lithium levels may not require additional antidepressant medications. However, patients maintaining low lithium levels or those who cannot tolerate high lithium levels may benefit from augmentation therapy with either paroxetine or imipramine. These findings suggest the need for additional studies of antidepressant treatment of bipolar depression, particularly in patients stabilized on lithium.

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REFERENCES

1. Kalin NH: Management of the depressive component of bipolar disorder. Depress Anxiety 1996/1997;4:190-198

2. Zornberg GL, Pope HG: Treatment of depression in bipolar disorder: new directions for research. J Clin Psychopharmacol 1993;13:397-408

3. Gelenberg AJ, Hopkins HS: Report on efficacy of treatments for bipolar disorder. Psychopharmacol Bull 1993;29:447-456

4. Sachs GS: Treatment-resistant bipolar depression. Psychiatr Clin North Am 1996;19:215-236

5. Schou M: Forty years of lithium treatment. Arch Gen Psychiatry 1997;54:9-13

6. Srisurapanont M, Yatham LN, Zis AP: Treatment of acute bipolar depression: a review of the literature. Can J Psychiatry 1995;40:S33-S44

7. Gershon S, Soares JC: Current therapeutic profile of lithium. Arch Gen Psychiatry 1997;54:16-20

8. Angst J, Stabl M: Efficacy of moclobemide in different patient groups: a meta-analysis of studies. Psychopharmacology 1992;106:S109-S113

9. Dantzler A, Salzman C: Treatment of bipolar depression. Psychiatr Serv 1995;46:229-230

10. Himmelhoch JM, Thase ME, Mallinger AG, Houck P: Tranylcypromine versus imipramine in anergic bipolar depression. Am J Psychiatry 1991;148:910-916

11. Prien RF, Kupfer DJ, Mansky PA, Small JG, Tuason VB, Voss CB, Johnson WE: Drug therapy in the prevention of recurrences in unipolar and bipolar affective disorders. Arch Gen Psychiatry 1984;41:1096-1104

12. Baumhackl U, Bizière K, Fischbach R, Geretsegger CH, Hebenstreit G, Radmayr E, Stabl M: Efficacy and tolerability of moclobemide compared with imipramine in depressive disorder (DSM-III): an Austrian double-blind, multicentre study. Br J Psychiatry 1989;155(suppl 6):78-83

13. Cohn JB, Collins G, Ashbrook E, Wernicke JF: A comparison of fluoxetine, imipramine, and placebo in patients with bipolar depressive disorder. Int Clin Psychopharmacol 1989;4:313-322

14. Sachs GS, Lafer B, Stoll AL, Banov M, Thibault AB, Tohen M, Rosenbaum JF: A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391-393

15. Bauer M, Zaninelli R, Muller-Oerlinghausen B, Meister W: Paroxetine and amitriptyline augmentation of lithium in the treatment of major depression: a double-blind study. J Clin Psychopharmacol 1999;19:164-171

16. Simpson SG, DePaulo JR: Fluoxetine treatment of bipolar II depression. J Clin Psychopharmcol 1991;11:52-54

17. Kasper S, Lepine JP, Mendlewicz J, Montgomery SA, Rush AJ Jr: Efficacy, safety, and indications for tricyclic and newer antidepressants. Depression 1994/1995;2:127-137

18. Sheline YI, Freedland KE, Carney RM: How safe are serotonin reuptake inhibitors for depression in patients with coronary heart disease? Am J Med 1997;102:54-59

19. Dilsaver SC, Swann AC: Mixed mania: apparent induction by a tricyclic antidepressant in five consecutively treated patients with bipolar depression. Biol Psychiatry 1995;37:60-62

20. Peet M: Induction of mania with selective serotonin re-uptake inhibitors and tricyclic antidepressants. Br J Psychiatry 1994;164:549-550

21. Stoll AL, Mayer PV, Kolbrener M, Goldstein E, Suplit B, Lucier J, Cohen BM, Tohen M: Antidepressant-associated mania: a controlled comparison with spontaneous mania. Am J Psychiatry 1994;151:1642-1645

22. Wehr TA, Goodwin FK: Rapid cycling in manic-depressives induced by tricyclic antidepressants. Arch Gen Psychiatry 1979;36:555-559

23. Fogelson DL, Bystritsky A, Pasnau R: Bupropion in the treatment of bipolar disorders: the same old story? J Clin Psychiatry 1992;53:443-446

24. Haykal RF, Akiskal HS: Bupropion as a promising approach to rapid cycling bipolar II patients. J Clin Psychiatry 1990;51:450-455

25. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56-62

26. Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Muller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T: Comparative efficacy of lithium and amitriptyline in the maintenance treatment of recurrent unipolar depression: a randomised study. J Affect Disord 1996;40:179-190

27. Greil W, Ludwig-Mayerhofer W, Erazo N, Engel RR, Czernik A, Giedke H, Muller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T: Lithium vs carbamazepine in the maintenance treatment of schizoaffective disorder: a randomised study. Eur Arch Psychiatry Clin Neurosci 1997;247:42-50

28. Greil W, Ludwig-Mayerhofer W, Erazo N, Schochlin C, Schmidt S, Engel RR, Czernik A, Giedke H, Müller-Oerlinghausen B, Osterheider M, Rudolf GA, Sauer H, Tegeler J, Wetterling T: Lithium versus carbamazepine in the maintenance treatment of bipolar disorders: a randomised study. J Affect Disord 1997;43:151-161

29. Tondo L, Mannu P, Silvetti F, Altamura C: Fluoxetine augmentation in bipolar disorder patients on maintenance lithium treatment. Int J Psychiatry Clin Pract 1997;1:203-206

30. Cohn JB, Wilcox CS: Paroxetine in major depression: a double-blind trial with imipramine and placebo. J Clin Psychiatry 1992;53(suppl):52-56

31. Gelenberg AJ, Jefferson JW: Lithium tremor. J Clin Psychiatry 1995;56:283-287

32. Vestergaard P, Poulstrup I, Schou M: Prospective studies on a lithium cohort, III: tremor, weight gain, diarrhea, psychological complaints. Acta Psychiatr Scand 1988;78:434-444

33. Gelenberg AJ, Kane JM, Keller MB, Lavori P, Rosenbaum JF, Cole K, Lavelle J: Comparison of standard and low serum levels of lithium for maintenance treatment of bipolar disorder. N Engl J Med 1989;321:1489-1493

34. Battegay R, Hager M, Rauchfleisch U: Double-blind comparative study of paroxetine and amitriptyline in depressed patients of a university psychiatric outpatient clinic (pilot study). Neuropsychobiology 1985;13:31-37

35. Dunbar GC, Cohn JB, Fabre LF, Feighner JP, Fieve RR, Mendels J, Shrivastava RK: A comparison of paroxetine, imipramine, and placebo in depressed out-patients. Br J Psychiatry 1991;159:394-398

36. Altshuler LL, Post RM, Leverich GS, Mikalauskas K, Rosoff A, Ackerman L: Antidepressant-induced mania and cycle acceleration: a controversy revisited. Am J Psychiatry 1995;152:1130-1138

37. Quitkin FM, Kane J, Rifkin A, Ramos-Lorenzi JR, Nayak DV: Prophylactic lithium carbonate with and without imipramine for bipolar 1 patients. Arch Gen Psychiatry 1981;38:902-907

38. Haenen J, De Bleeker E, Mertens C, Batholome F, Pardoen D, Stellamans G, Leyman S, Schotte G. An interaction study of paroxetine on lithium plasma levels in depressed patients stabilised on lithium therapy. Eur J Clin Res 1995;7:161-167

39. Post RM, Uhde TW: Carbamazepine as a treatment for refractory depressive illness and rapid cycling manic-depressive illness. In Treating Resistant Depression. Edited by Zohar JH, Belmaker RH. New York, NY, PMS Publishing Co, 1987:175-235

Table 1. Demographic and Clinical Characteristics of Patients With Bipolar Disorder Currently in a Depressive Episode Who Received Paroxetine, Imipramine, or Placebo

Characteristics	Paroxetine N=35 (%)		Imipramine N=39 (%)		Placebo N=43 (%)	
Mean age (years)	42.5		41.9		40.4	
Age range (years)	24-66		21-71		21-66	
Gender						
Female	19	54.3	23	59.0	23	53.5
Male	16	45.7	16	41.0	20	46.5
Race						
Caucasian	34	97.1	39	100.0	39	90.7
Other	1	2.9	0	0.0	4	9.3

Table 2. Mean Baseline and Mean Baseline Change Values of Hamilton Rating Scale for Depression (HAMD-17) and the Clinical Global Impressions (CGI) Severity of Illness Scale

	Paroxetine				Imipramine				Placebo				Treatment p-values (F Value)[a]		
	N	Mean Baseline	Mean Change	SD	N	Mean Baseline	Mean Change	SD	N	Mean Baseline	Mean Change	SD	PAR vs PLA	IMP vs PLA	PAR vs IMP
Total response dataset															
HAMD	33	20.38	-10.2	7.30	36	20.71	-10.1	7.26	43	21.57	-8.06	7.28	0.199 (1.67)	0.220 (1.52)	0.932 (0.01)
CGI	33	4.21	-1.33	1.38	36	4.31	-1.28	1.38	43	4.33	-0.91	1.38	0.196 (1.70)	0.245 (1.37)	0.876 (0.02)
High-serum lithium level dataset[b]															
HAMD	14	20.29	-9.79	7.11	17	21.35	-9.35	7.09	21	21.95	-10.4	7.10	0.809 (0.06)	0.659 (0.20)	0.867 (0.03)
CGI	14	4.21	-1.14	1.42	17	4.35	-0.94	1.44	21	4.29	-1.24	1.42	0.849 (0.04)	0.528 (0.40)	0.698 (0.15)
Low-serum lithium level dataset[b]															
HAMD	19	20.37	-10.4	7.28	19	20.11	-10.7	7.28	22	21.18	-5.82	7.32	0.049[c] (4.06)	0.038[c] (4.53)	0.912 (0.01)
CGI	19	4.21	-1.47	1.35	19	4.26	-1.58	1.35	22	4.36	-0.59	1.36	0.040[c] (4.41)	0.022[c] (5.52)	0.810 (0.06)

IMP = imipramine; PAR = paroxetine; PLA = placebo; SD = standard deviation.

[a]Serum lithium level >0.8 mEq/L.

[b]Serum lithium level ≤0.8 mEq/L.

[c]Significant for α=0.05 (analysis of variance using model with effects for treatment).

[d] df for total response dataset = 1, 106; df for high-serum lithium level dataset = 1, 49; df for low-serum lithium level dataset = 1, 57.

FIGURE LEGENDS

Figure. Mean serum lithium concentrations in paroxetine, imipramine, and placebo groups.

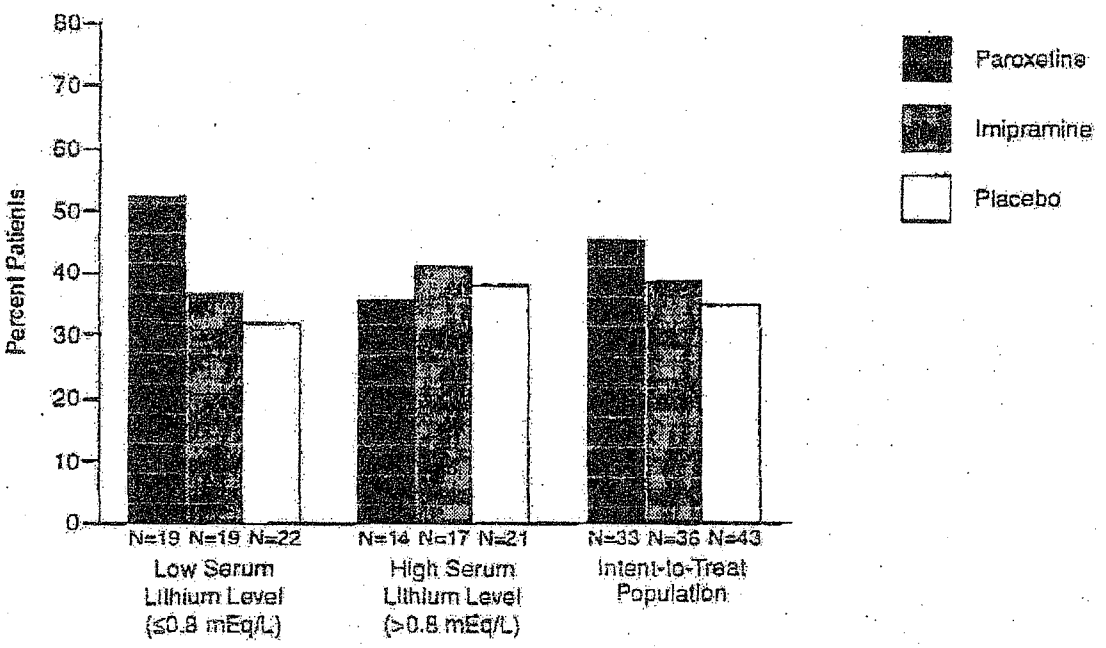
80
70
60
50
40
30
20
10
0
Percent Patients
N=19 N=19 N=22
Low Serum Lithium Level (≤0.8 mEq/L)
N=14 N=17 N=21
High Serum Lithium Level (>0.8 mEq/L)
N=33 N=36 N=43
Intent-to-Treat Population
Paroxetine
Imipramine
Placebo

Figure 1.

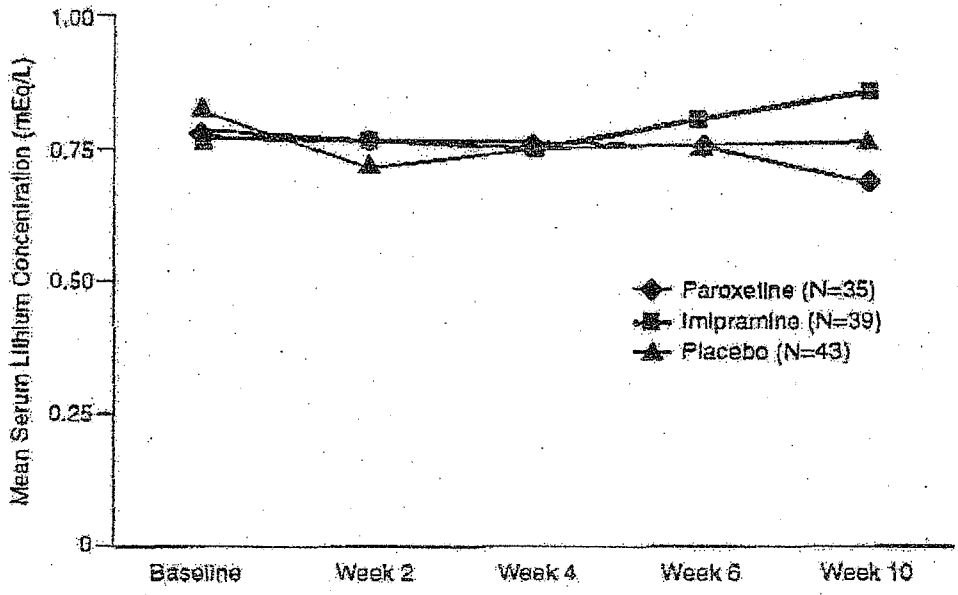
1.00
0.75
0.50
0.25
0
Mean Serum Lithium Concentration (mEq/L)
Baseline
Week 2
Week 4
Week 6
Week 10
Paroxetine (N=35)
Imipramine (N=39)
Placebo (N=43)

Figure 2.

Attachment E

Impugning the Integrity of Medical Science
The Adverse Effects of Industry Influence

Catherine D. DeAngelis, MD, MPH
Phil B. Fontanarosa, MD, MBA

THE PROFESSION OF MEDICINE, IN EVERY ASPECT—clinical, education, and research—has been inundated with profound influence from the pharmaceutical and medical device industries. This has occurred because physicians have allowed it to happen, and it is time to stop.

Two articles[1,2] in this issue of *JAMA* provide a glimpse of one company's apparent misrepresentation of research data and its manipulation of clinical research articles and clinical reviews; such information and articles influence the education and clinical practice of physicians and other health professionals. The direct influence of for-profit companies on education[3-6] and clinical practice[7,8] has been well documented, so this Editorial deals primarily with clinical research.

The articles by Ross and colleagues[1] and by Psaty and Kronmal[2] document how one company, Merck & Co Inc, apparently manipulated dozens of publications to promote one of its products. But make no mistake—the manipulation of study results, authors, editors, and reviewers is not the sole purview of one company.[9-12] In this case, documents that provided evidence necessary to demonstrate the manipulation became public (and publishable) because of litigation involving one of that company's products, rofecoxib. As disclosed in the articles,[1,2] all authors, except one, report having served as paid consultants for plaintiffs in litigation against Merck. However, at our insistence the authors of both studies have made all documents used in their articles available on the Internet and have provided the information necessary to access those documents (ie, Web site addresses) in the articles. Thus, anyone questioning the veracity or interpretation of the information in these 2 articles,[1,2] or wishing to inspect the documents referenced in these 2 articles, will have ready access to the materials.

The study by Ross et al[1] illustrates that clinical trial articles and review articles related to rofecoxib frequently were written by unacknowledged authors who were employees of for-profit information industries, and often attributed first (or primary) authorship to academically affiliated investigators who either had little to do with the study or review or who did not disclose financial support from the company. It is important to note that for some of the referenced publications listed in the Table of the article by Ross et al,[1] some of the authors either did not actually receive financial support from the company; were not required by the journal in which the study was published to disclose their financial support or relationship with the sponsor; did report their financial support or relationship with the sponsor, but the journal chose not to publish those author disclosures; or did disclose their financial support, and those disclosures were published.

However, it is clear that at least some of the authors played little direct roles in the study or review, yet still allowed themselves to be named as authors. Individuals, particularly physicians, who allow themselves to be used in this way, especially for financial gain, manifest a behavior that is unprofessional and demeaning to the medical profession and to scientific research.

The study by Psaty and Kronmal,[2] which is based on analysis of published articles, information provided by the company to the US Food and Drug Administration (FDA), and the company's own internal analysis, shows how Merck may have misrepresented the risk-benefit profile of rofecoxib in clinical trials involving patients with Alzheimer disease or dementia. The authors show that the company's report to the FDA appears to have attempted to minimize the mortality risk by using an "as-treated" analysis, whereas an internal analysis conducted by the company several months earlier and using the correct intention-to-treat analysis provided evidence of a significantly increased mortality risk among patients assigned to receive rofecoxib. The authors also report that, for at least 1 rofecoxib trial, company documents reveal that there had been no data and safety monitoring board in place, thereby potentially endangering patients who participated in this study. Moreover, as Ross et al[1] describe in their evaluation of this same trial (Figure 2 in their article), the data analysis for this study may have been completed before the academically affiliated authors were involved with the manuscript; this may not be surprising, given that 8 of the 11 authors named in the byline of the published article are identified as being Merck employees.

Journal editors also bear some of the responsibility for enabling companies to manipulate publications. Some editors may allow articles and supplements to be published without requiring complete disclosure of individual financial support, and without requiring clear and complete disclosure of industry support of and direct involvement with research ar-

See also pp 1800 and 1813.

Author Affiliations: Dr DeAngelis is Editor in Chief (cathy.deangelis@jama-archives.org) and Dr Fontanarosa is Executive Deputy Editor, *JAMA*.

ticles or reviews. But even when disclosure is required and closely monitored, manipulation can still occur. For example, Figure 3 in Ross et al[1] includes a cover letter (dated October 2000) from Scientific Therapeutics Information Inc for the delivery of a manuscript " . . . to be submitted to *JAMA* Express." The study was, indeed, published in *JAMA* (in January 2002),[13] but not as an Express article. In that publication, it was disclosed that Merck sponsored the trial; that 3 of the 5 authors (including the first and corresponding author) were employees of Merck; and that the other 2 authors (who were identified as the coprincipal investigators) disclosed receiving funding from Merck. However, there was no disclosure that the manuscript had been written by Scientific Therapeutics Information Inc, a company specializing in the development of scientific literature,[14] ie, writing papers for a price.

Perhaps some editors, investigators, reviewers, and readers would see little or no harm in this failed disclosure because all other disclosures were made. However, if there was nothing to hide, why were the names (and affiliations) of the individuals who actually wrote at least the first draft of the manuscript omitted? Experienced authors know that the initial draft (in this case paid for by Merck) sets the tone for the manuscript. Moreover, it is unfair to the authors of the first draft not to provide them with credit for their work.[15,16] Another problem with failing to disclose "ghost writers" is that there is a reasonable assumption that the principal investigator was involved with writing the manuscript from the beginning. If a professional (ghost) writer is listed as an author, the issue becomes determining when the principal investigator became involved in the study. Even with the requirement for registering clinical trials,[17] identifying the principal investigator is not one of the required elements in the registration information fields. It might be advantageous for including the names of the principal investigator(s) to become a requirement in trial registration, even though the vast majority of medical journals do not require registration of clinical trials.

It can be argued that merely disclosing relationships with for-profit companies and identifying who actually writes articles for publication does little to stop the practices for cases in which the relationships are unethical or in which the sponsor has inappropriate influence over the data or control over the manuscript. However, disclosure does provide readers with information that can be used in deciding about the credibility of the article—at least as interpreted by the reader. Full disclosure also might prove too embarrassing to authors who might reconsider lending their name and reputations to articles in which they did not meet requirements for authorship.

The article by Psaty and Kronmal[2] also represents another example of problems with data misrepresentation, data analysis, and selective reporting in industry-sponsored studies.[9,18] In an effort to counteract such problems, in 2001 *JAMA* began to require that for all studies, an academic investigator who is not employed by the sponsor must attest that he or she "had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis."[19] In addition, for studies that are financially supported by for-profit companies, *JAMA* began to require that the data analysis must be conducted independently by an academic statistician who is not an employee of the sponsor and who is at an academic center, such as a medical school, or is an employee of a government research institute.[19] This approach provides an additional layer of oversight for the integrity of the data analysis and reporting, such that if concerns about data manipulation or misrepresentation arise, a mechanism for investigation would be in place, such as by investigative committees appointed by the dean of the academic medical center at which the independent statistician is a faculty member. If all journals would have similar policies,[20] the likelihood of manipulation of data, inappropriate data analysis, and selective reporting of results could be substantially decreased.

Another source that may contribute to the manipulation of research studies involves peer reviewers who have relationships with industry. Such reviewers may provide biased reviews that favor products of companies with which they have strong financial relationships, may fail to disclose their conflicts of interest to journal editors, or may even provide for-profit companies with confidential information obtained during the peer review process. For example, it was recently reported that a peer reviewer for the *New England Journal of Medicine* sent a confidential manuscript that he was invited to review and that demonstrated an increased mortality risk associated with rosiglitazone to the manufacturer of this drug weeks ahead of the publication.[21] Even though most journals require reviewers to disclose potential conflicts of interest, and editors must consider those disclosures in authorizing reviewers to complete reviews, actions such as this constitute a breach of trust and a violation of the ethical principles and confidentiality on which the peer review process is based.

What are the lessons from the 2 articles[1,2] in this issue of *JAMA*, from other publications that have examined related issues,[11,12] and from extensive experience with how clinical research has been manipulated by for-profit companies? First, manipulation of studies and misrepresentation of study results could not occur without the cooperation (active and tacit) of clinical researchers, other authors, journal editors, peer reviewers, and the FDA. Second, public trust for clinical research is in great jeopardy especially when the extent of how widespread such practices have become is unknown. Although we truly believe that the vast majority of researchers and other authors are honest and have the highest scientific integrity, manipulation of studies and publications by the pharmaceutical and medical device industries is either increasing or there has been more exposure of these practices. Third, in addition to clinical research, clinical practice and medical education also are greatly influenced by for-profit companies. Drastic action is essential, and cooperation of everyone involved in medical research, medical editing, medical education, and clinical practice is required for meaningful change to occur.

As a beginning, we propose the following:

1. All clinical trials must be prospectively listed in registries accepted by the International Committee of Medical Journal Editors (ICMJE) prior to patient enrollment, and the name(s) of the principal investigator(s) should be included as a required data element in the trial registration record.

2. All individuals named as authors on articles must fulfill authorship criteria. Journals should require each author to report his or her specific contributions to the article, and should consider publishing these contributions. All individuals who were involved with the manuscript or study but who do not qualify for authorship (such as those who provided writing assistance) must be named in the acknowledgment section of the article, with reporting of their specific affiliations and contributions and whether they were compensated for those contributions.

3. All journals must disclose all pertinent relationships of all authors with any for-profit companies, and must publish all funding sources for each article.

4. Journal editors must seriously consider funding sources and authors' disclosed financial conflicts of interest and financial relationships when deciding whether to publish a study or review.

5. For-profit companies that sponsor biomedical research studies should not be solely or primarily involved in collecting and monitoring of data, in conducting the data analysis, and in preparing the manuscript reporting study results. These responsibilities should primarily or solely be performed by academic investigators who are not employed by the company sponsoring the research.

6. All journals must require a statistical analysis of clinical trial data conducted by a statistician who is not an employee of a for-profit company.

7. Any author who fails to disclose financial relationships or other conflicts of interest, or who allows his or her name to be used for work that he or she did not actually perform, must be reported to the appropriate authority (ie, medical school dean or department chair) or appropriate oversight body. If an article in which this occurs is published, the offending author must then submit a letter to the editor, in which he or she provides full disclosure and apologizes for the infraction to the readers of the journal. Depending on the nature and severity of the issue, the author may be banned from publishing articles in that journal.

8. Any peer reviewer who provides any confidential information, such as a manuscript under review, to any third parties, such as for-profit companies, or who engages in other similar unethical behavior, also should be reported to the appropriate authority (eg, medical school dean) or oversight body, and should be banned from reviewing and publishing articles in that journal.

9. Any editor who knowingly allows (or is party to allowing) for-profit companies to manipulate his or her journal must be relieved of the editorship.

10. To maintain a healthy distance from industry influence, professional organizations and providers of continuing medical education courses should not condone or tolerate for-profit companies having any input into the content of educational materials or providing funding or sponsorship for medical education programs.

11. Individual physicians must be free of financial influences of pharmaceutical and medical device companies including serving on speaker's bureaus or accepting gifts.

Primum non nocere does not only hold true for physicians directly treating patients, but also holds true for all involved in medical research, biomedical publication, and medical education. When integrity in medical science or practice is impugned or threatened—such as by the influence of industry—patients, clinicians, and researchers are all at risk for harm, and public trust in research is jeopardized. Ensuring, maintaining, and strengthening the integrity of medical science must be a priority for everyone.

Financial Disclosures: None reported.

REFERENCES

1. Ross JS, Hill KP, Egilman DS, Krumholz HM. Guest authorship and ghostwriting in publications related to rofecoxib: a case study of industry documents from rofecoxib litigation. *JAMA*. 2008;299(15):1800-1812.
2. Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. *JAMA*. 2008;299(15):1813-1817.
3. DeAngelis C. Rainbow to dark clouds. *JAMA*. 2005;294:1107.
4. Wazana A. Physicians and the pharmaceutical industry. *JAMA*. 2000;283 (3):373-380.
5. Steinbrook R. Financial support of continuing medical education. *JAMA*. 2008; 299(9):1060-1062.
6. Fletcher SW. *Chairman's Summary of the Conference: Continuing Education in the Health Professions: Improving Healthcare Through Lifelong Learning*. New York, NY: Josiah Macy Jr Foundation; 2008.
7. Choudhry NK, Stelfox HT, Detsky AS. Relationships between authors of clinical practice guidelines and the pharmaceutical industry. *JAMA*. 2002;287(5): 612-617.
8. Carlat D. Dr drug rep. *New York Times Magazine*. November 25, 2007.
9. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. *JAMA*. 2000;284(10):1247-1255.
10. Solomon DH, Avorn J. Coxibs, science, and the public trust. *Arch Intern Med*. 2005;165(2):158-160.
11. Steinman MA, Bero LA, Chren MM, Landefeld CS. Narrative review: the promotion of gabapentin. *Ann Intern Med*. 2006;145(4):284-293.
12. Healy D, Cattel D. Interface between authorship, industry and science in the domain of therapeutics. *Br J Psychiatry*. 2003;183:22-27.
13. Geba GP, Weaver AL, Polis AB, et al. Efficacy of rofecoxib, celecoxib, and acetaminophen in osteoarthritis of the knee. *JAMA*. 2002;287(1):64-71.
14. Scientific Therapeutics Information Inc Web site. http://www.stimedinfo.com /sti.htm. Accessibility verified March 21, 2008.
15. International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. http://www.icmje.org. Accessibility verified March 21, 2008.
16. Rennie D, Flanagin A. Authorship! authorship! guests, ghosts, grafters, and the two-sided coin. *JAMA*. 1994;271(6):469-471.
17. DeAngelis CD, Drazen JM, Frizelle FA, et al. Clinical trial registration. *JAMA*. 2004;292(11):1363-1364.
18. Curfman GD, Morrisey S, Drazen JM. Expression of concern: Bombardier et al., "Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis," *N Engl J Med* 2000;343:1520-8. *N Engl J Med*. 2005;353(26):2813-2814.
19. DeAngelis CD, Fontanarosa PB, Flanagin A. Reporting financial conflicts of interest and relationships between investigators and research sponsors. *JAMA*. 2001; 286(1):89-91.
20. Fontanarosa PB, Flanagin A, DeAngelis CD. Reporting conflicts of interest, financial aspects of research, and role of sponsors in funded studies. *JAMA*. 2005; 294(1):110-111.
21. Vastag B. Reviewer leaked Avandia study to drug firm. *Nature*. 2008;451 (7178):509.

Attachment F

Search Results

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Page 1 of 1

Project Number	Sub #	Project Title	Contact Principal Investigator	Organization	FY	Admin IC	Funding IC	FY Total Cost by IC
5R24MH051761-05	9002	CORE--NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	BONSALL, ROBERT W.	EMORY UNIVERSITY	1998	NIMH		
5R24MH051761-04	9002	CORE--NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	BONSALL, ROBERT W.	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-03	9002	CORE--NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	BONSALL, ROBERT W.		1996	NIMH		
5R24MH051761-05	9001	CORE--PATIENT RECRUITMENT AND ASSESSMENT	GOODMAN, SHERRYL	EMORY UNIVERSITY	1998	NIMH		
5R24MH051761-04	9001	CORE--PATIENT RECRUITMENT AND ASSESSMENT	GOODMAN, SHERRYL	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-03	9001	CORE--PATIENT RECRUITMENT AND ASSESSMENT	GOODMAN, SHERRYL		1996	NIMH		
5R24MH051761-05	9004	CORE--EXPERIMENTAL DESIGN AND BIOSTATISTICS	MARSTELLER, FREDERICK A	EMORY UNIVERSITY	1998	NIMH		
5R24MH051761-04	9004	CORE--EXPERIMENTAL DESIGN AND BIOSTATISTICS	MARSTELLER, FREDERICK A	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-03	9004	CORE--EXPERIMENTAL DESIGN AND BIOSTATISTICS	MARSTELLER, FREDERICK A		1996	NIMH		
5R24MH051761-05	9003	CORE--BIOLOGICAL TISSUES AND FLUIDS	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1998	NIMH		
5R24MH051761-05		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1998	NIMH		
5R24MH051761-04	9003	CORE--BIOLOGICAL TISSUES AND FLUIDS	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-04		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1997	NIMH		
3R24MH051761-04S1		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-03	9003	CORE--BIOLOGICAL TISSUES AND FLUIDS	NEMEROFF, CHARLES B		1996	NIMH		
5R24MH051761-03		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1996	NIMH		
5R24MH051761-02		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1995	NIMH		
1R24MH051761-01A1		INFRASTRUCTURE SUPPORT PROGRAM	NEMEROFF, CHARLES B	EMORY UNIVERSITY	1994	NIMH		
5R24MH051761-04S1	9001	CORE--PATIENT RECRUITMENT AND ASSESSMENT	Unavailable	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-04S1	9002	CORE--NEUROENDOCRINOLOGY, NEUROCHEMISTRY, AND BRAIN IMAGING	Unavailable	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-04S1	9003	CORE--BIOLOGICAL TISSUES AND FLUIDS	Unavailable	EMORY UNIVERSITY	1997	NIMH		
5R24MH051761-04S1	9004	CORE--EXPERIMENTAL DESIGN AND BIOSTATISTICS	Unavailable	EMORY UNIVERSITY	1997	NIMH		

Page 1 of 1

Attachment G

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
Bethesda, Maryland 20892

FEB 17 2011

Mr. Paul Thacker
Investigator
Project On Government Oversight
1100 G Street, NW, Suite 900
Washington, DC 20005-3806

Dear Mr. Thacker:

Thank you for your letter of November 29, 2010, in which you express your concern about financial conflicts of interest and ghostwriting in academia, particularly in medical schools.

I want to state clearly that the National Institutes of Health (NIH) does not condone the practice of ghostwriting, particularly situations in which investigators may have accepted payment from private entities in return for allowing their names to be used as authors on publications in which they had very limited input. In fact, NIH's Intramural Research Program has authorship guidelines that are comparable to those described in the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals*, which were developed by the Internal Committee of Medical Journal Editors.

While the NIH extramural policy governing NIH grantees does not use the term ghostwriting, Federal regulations and policies relating to Public Health Service (PHS)-supported research could be applicable to ghostwriting, depending on the specific circumstances of a particular case. For example, a case of ghostwriting involving NIH-funded researchers may be appropriate for consideration as a case of plagiarism; i.e., the appropriation of another person's ideas, processes, results, or words without giving appropriate credit; or fabrication, i.e., making up data or results and recording or reporting them. Such a case would be handled by the Office of Research Integrity (ORI) of the Department of Health and Human Services (HHS), which investigates research misconduct as defined in the PHS's 42 C.F.R. Parts 50 and 93, *Policies on Research Misconduct and the Final Rule*. If ORI makes a finding of research misconduct, the NIH may take appropriate enforcement action(s), which could include modification of the terms of the award, suspension, termination, withholding of support, temporary withholding of payment, conversion from an advance payment method to a reimbursement method, or debarment, among other options.

The NIH believes that ghostwriting should be addressed when scientific articles citing extramural Federal funding are submitted to journals for publication. Current policy requires all HHS grantees to acknowledge Federal funding when issuing statements, press releases, requests for proposals, bid invitations, and other documents describing projects or programs funded in whole or in part with Federal money. However, it does not require that all parties who contribute to a publication, including those that contribute financially, be acknowledged. The NIH is considering how best to address the issue of ghostwriting in the development and authorship of medical literature arising from Federal research funding.

As you are aware, the NIH, on behalf of HHS and the PHS, is engaged in the rulemaking process to revise the regulations governing investigator financial conflict-of-interest (42 CFR Part 50 Subpart F, *Responsibility of Applicants for Promoting Objectivity in Research for which PHS Funding is Sought* and 45 CFR Part 94, *Responsible Prospective Contractors*). Because of its potential to create conflicts-of-interest that could bias or otherwise inappropriately influence NIH-supported research, "paid authorship" was specifically included in the proposed revisions to the regulations. By including "paid authorship" in the definition of "Significant Financial Interest" in the proposed rule, the NIH is sending a clear message to institutions and investigators alike that we support the principles of transparency and accountability in research and that institutions and investigators engaging in such activity may be subject to more rigorous disclosure and reporting. The proposed rule may be accessed at http://www.regulations.gov/search/Regs/home.html#documentDetail?R=0900006480af37ce.

The NIH is committed to preserving the public trust in the objectivity of NIH-supported research, and we strongly believe that all research should be conducted with the highest scientific and ethical standards. Thus, we have proposed substantial changes to the existing financial conflict-of-interest regulations to increase accountability and transparency, which are vital to managing the essential relationships between Government, NIH-funded research institutions, and the private sector.

Thank you again for your interest in the NIH and our programs. I am also sending this response to Ms. Brian.

Sincerely yours,

Francis S. Collins, M.D., Ph.D.
Director

Attachment H

The NEW ENGLAND JOURNAL of MEDICINE

Effectiveness of Adjunctive Antidepressant Treatment for Bipolar Depression

Gary S. Sachs, M.D., Andrew A. Nierenberg, M.D., Joseph R. Calabrese, M.D., Lauren B. Marangell, M.D., Stephen R. Wisniewski, Ph.D., Laszlo Gyulai, M.D., Edward S. Friedman, M.D., Charles L. Bowden, M.D., Mark D. Fossey, M.D., Michael J. Ostacher, M.D., M.P.H., Terence A. Ketter, M.D., Jayendra Patel, M.D., Peter Hauser, M.D., Daniel Rapport, M.D., James M. Martinez, M.D., Michael H. Allen, M.D., David J. Miklowitz, Ph.D., Michael W. Otto, Ph.D., Ellen B. Dennehy, Ph.D., and Michael E. Thase, M.D.

ABSTRACT

BACKGROUND

Episodes of depression are the most frequent cause of disability among patients with bipolar disorder. The effectiveness and safety of standard antidepressant agents for depressive episodes associated with bipolar disorder (bipolar depression) have not been well studied. Our study was designed to determine whether adjunctive antidepressant therapy reduces symptoms of bipolar depression without increasing the risk of mania.

METHODS

In this double-blind, placebo-controlled study, we randomly assigned subjects with bipolar depression to receive up to 26 weeks of treatment with a mood stabilizer plus adjunctive antidepressant therapy or a mood stabilizer plus a matching placebo, under conditions generalizable to routine clinical care. A standardized clinical monitoring form adapted from the mood-disorder modules of the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, was used at all follow-up visits. The primary outcome was the percentage of subjects in each treatment group meeting the criterion for a durable recovery (8 consecutive weeks of euthymia). Secondary effectiveness outcomes and rates of treatment-emergent affective switch (a switch to mania or hypomania early in the course of treatment) were also examined.

RESULTS

Forty-two of the 179 subjects (23.5%) receiving a mood stabilizer plus adjunctive antidepressant therapy had a durable recovery, as did 51 of the 187 subjects (27.3%) receiving a mood stabilizer plus a matching placebo ($P=0.40$). Modest nonsignificant trends favoring the group receiving a mood stabilizer plus placebo were observed across the secondary outcomes. Rates of treatment-emergent affective switch were similar in the two groups.

CONCLUSIONS

The use of adjunctive, standard antidepressant medication, as compared with the use of mood stabilizers, was not associated with increased efficacy or with increased risk of treatment-emergent affective switch. Longer-term outcome studies are needed to fully assess the benefits and risks of antidepressant therapy for bipolar disorder. (ClinicalTrials.gov number, NCT00012558.)

From Massachusetts General Hospital, Harvard Medical School (G.S.S., A.A.N., M.J.O.), and Boston University (M.W.O.) — all in Boston; Case Western Reserve University–University Hospitals Case Medical Center, Cleveland (J.R.C.); Baylor College of Medicine and South Central Mental Illness Research Education and Clinical Core — both in Houston (L.B.M., J.M.M.); the University of Pittsburgh (S.R.W.) and University of Pittsburgh School of Medicine (E.S.F., M.E.T.) — both in Pittsburgh; the University of Pennsylvania, Philadelphia (L.G.); the University of Texas Health Science Center, San Antonio (C.L.B.); the University of Oklahoma College of Medicine–Tulsa, Tulsa (M.D.F.); Stanford University School of Medicine, Stanford, CA (T.A.K.); the University of Massachusetts Medical School, Worcester (J.P.); the Portland Veterans Affairs Medical Center and Oregon Health and Sciences University — both in Portland (P.H.); the University of Toledo College of Medicine, Toledo, OH (D.R.); the University of Colorado Health Sciences Center, Denver (M.H.A.); the University of Colorado, Boulder, and University of Colorado Health Sciences Center, Boulder (D.J.M.); and Purdue University, West Lafayette, IN (E.B.D.). Address reprint requests to Dr. Sachs at the Bipolar Clinic and Research Program, Massachusetts General Hospital, 50 Staniford St., Suite 580, Boston, MA 02114, or at gsachs@partners.org.

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Bipolar disorder, the sixth-leading cause of disability worldwide,[1] is a chronic and recurrent psychiatric illness with a lifetime prevalence of just under 4%[2] and annual costs that exceed those of diabetes or recurrent (unipolar) major depressive disorder.[3] Although abnormal mood elevation is the cardinal diagnostic feature that distinguishes bipolar disorder from recurrent major depressive disorder, depression that alternates with manic episodes (bipolar depression) is the leading cause of impairment and death among patients with bipolar disorders.[4-6]

Two main limitations related to standard antidepressant medications hamper their use in the treatment of bipolar depression. First, though these agents have proved to be efficacious in treating unipolar depression, the data providing support for their use in treating bipolar depression are minimal and are not considered to be sufficient to guide clinical practice. Second, the widely held belief that antidepressants can induce new episodes of abnormal mood elevation or accelerate the rate of cycling has been neither confirmed nor refuted by placebo-controlled studies.

Adequately powered, well-controlled studies are needed to show the effectiveness of treatments for bipolar depression under conditions of routine clinical practice. Pivotal studies sponsored by pharmaceutical companies are designed primarily to demonstrate efficacy for purposes of regulatory approval. These studies typically involve narrow eligibility requirements and short-term cross-sectional outcomes, which limit the generalizability of the results to routine clinical practice.

The Food and Drug Administration (FDA) has not approved any of the more than 25 standard antidepressants for the treatment of bipolar depression. However, standard antidepressants are commonly used as adjuncts to mood-stabilizing medication for the treatment of bipolar depression, despite limited evidence of the short-term and long-term efficacies and the putative risk of treatment-emergent mania or hypomania.[7-10] Furthermore, in a placebo-controlled study in which subjects using therapeutic doses of the mood stabilizer lithium were randomly assigned to receive concurrent treatment with a standard antidepressant (paroxetine or imipramine) or placebo, those receiving lithium plus an antidepressant did not have a significant advantage over those receiving lithium plus placebo.[11] Indeed, the only large positive trial of standard antidepressant treatment for bipolar depression published to date involved combination treatment with an atypical antipsychotic drug, rather than a traditional (non–dopamine blocking) mood stabilizer.[12] In that study, the combination of olanzapine and fluoxetine was superior to placebo as well as to olanzapine alone. However, the study did not address the effectiveness of standard antidepressants used in conjunction with lithium or valproate; thus, its results may not be generalizable to the treatment of patients with bipolar depression who typically seek treatment.

The Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) is a collaboration sponsored by the National Institute of Mental Health designed to evaluate the effectiveness of treatments for bipolar disorder and to provide results that are generalizable to routine clinical practice.[13] STEP-BD recruited a representative group of patients with bipolar disorder who were seeking treatment and used clinically meaningful outcomes. We report results from a controlled trial within STEP-BD evaluating the effectiveness of standard antidepressants for the short-term treatment of major depressive episodes in patients with bipolar disorder.

METHODS

The STEP-BD collaborators conducted this multicenter, double-blind, randomized, placebo-controlled, parallel-group study of standard antidepressants (either bupropion or paroxetine) as adjuncts to treatment with mood stabilizers (lithium, valproate, carbamazepine, or other FDA-approved antimanic agents) at 22 centers in the United States between November 1999 and July 2005. Subjects with bipolar I or bipolar II disorder were treated for up to 26 weeks to evaluate the effectiveness, safety, and tolerability of the adjunctive use of antidepressant medication. The study was approved by the institutional review board at each site and was overseen by a data and safety monitoring board.

The rationale for the design and methods of the STEP-BD trials has been described previously.[13] The STEP-BD protocol was critiqued by a committee of external experts and consumer advocates and was posted for public review.

SELECTION OF SUBJECTS

Study subjects were at least 18 years old and met the criteria of the *Diagnostic and Statistical Manual of Mental Disorders,* fourth edition (DSM-IV), for a ma-

jor depressive episode associated with bipolar I or bipolar II disorder. The diagnosis of bipolar disorder was confirmed at entry into STEP-BD by using an affective disorder evaluation form adapted from the Structured Clinical Interview for DSM-IV[14] and by the independent administration of the Mini-International Neuropsychiatric Interview.[15] We excluded subjects with a history of intolerance or nonresponse to both bupropion and paroxetine, as well as those requiring current short-term treatment for a coexisting substance-abuse disorder or requiring the addition of antipsychotic medication or a change in the dose of a long-term antipsychotic medication. Subjects enrolled in STEP-BD provided additional written informed consent for our study. At the time of randomization, all subjects agreed to receive a concomitant mood stabilizer.

INTERVENTIONS

Subjects were assigned to double-blind treatment with a mood stabilizer plus an adjunctive antidepressant or a mood stabilizer plus a matching placebo with the use of an equipoise-stratified randomization method.[16] This method enabled treating psychiatrists to choose from three randomization strata (placebo vs. bupropion, placebo vs. paroxetine, and placebo vs. either antidepressant) and thus allowed for the inclusion of subjects with a clear preference for a given antidepressant. STEP-BD clinicians, trained and certified in the use of a clinical monitoring form and other study scales, selected the mood stabilizers and managed all medications.[12]

Paroxetine and bupropion were selected to represent the standard antidepressants most commonly prescribed for bipolar depression, since these agents have different mechanisms of action and adverse-effect profiles.[9,11,16,17] Use of these antidepressants is associated with low rates of switch to mania or hypomania early in the course of treatment (treatment-emergent affective switch). Mood stabilizers were initially limited to lithium, valproate, the combination of lithium and valproate, or carbamazepine. In 2004, the protocol was amended to define mood stabilizers operationally as any FDA-approved antimanic agent.

Mood-stabilizing medications were adjusted clinically to target the therapeutic range for each drug. Standard antidepressant medications in use at randomization were tapered by at least 50% during the first week after randomization and were not permitted after the second week. All other clinically indicated medications were permitted. Subjects also had the option of remaining with their nonstudy psychotherapist, of having no psychosocial intervention, or of being enrolled into a STEP-BD trial comparing long-term (intensive) psychosocial interventions with a short-term (brief) psychoeducational intervention.[18]

Paroxetine or matching placebo was initiated at 10 mg daily and increased to a maximum of 40 mg daily. A sustained-release preparation of bupropion or matching placebo was initiated at 150 mg daily and increased to a maximum of 375 mg daily. Four follow-up assessments were scheduled over the first 6 weeks. Subjects who had severe adverse effects or met criteria for hypomania or mania discontinued the antidepressant or placebo and received open treatment while remaining in STEP-BD. After 6 weeks, subjects who had a response continued the double-blind treatment with monthly follow-up for up to 20 more weeks; those who did not were offered further increases in the dose of the antidepressant or placebo or open-label increase in the dose, with follow-up scheduled at 2-week intervals over the next 10 weeks.

EFFECTIVENESS OUTCOMES

At study entry, subjects were assessed with the use of the Clinical Monitoring Form for mood disorders[19] and formal mood-rating scales. The Clinical Monitoring Form is a composite assessment tool developed for use in clinical practice; it includes a version of the current mood modules of the Structured Clinical Interview for DSM-IV, modified to include continuous symptom subscales for depression (SUM-D) and mood elevation (SUM-ME), in addition to questions about categorical outcomes. SUM-D scores range from 0 to 22 and SUM-ME scores range from 0 to 16; higher scores indicate more severe symptoms. The SUM-D and SUM-ME subscales are well correlated with formal rating scales: the Montgomery–Asberg Depression Rating Scale and the Young Mania Rating Scale, respectively.[19] The formal rating scales were administered by independent raters at study entry and also quarterly, for quality control. The Clinical Monitoring Form was administered at every follow-up visit.

The a priori primary outcome was durable recovery, defined as euthymia for at least 8 consecutive weeks. Subjects were also classified on the basis of secondary outcomes, defined in Table 1. Treatment-effectiveness response rates were based on subjects whose SUM-D scores improved by at

Table 1. Effectiveness Outcomes.

Outcome	Definition	Time Frame	Comment
Durable recovery (primary outcome)	At least 8 consecutive weeks of euthymia (no more than two depressive or two manic symptoms)	Onset by 16 wk	Consistent with the DSM-IV definition of recovery
Transient remission	1–7 Consecutive weeks of euthymia	Onset by 16 wk	DSM-IV criteria for hypomania and mania not met
Treatment-emergent affective switch	DSM-IV criteria for hypomania or mania met or intervention by treating clinician for clinically significant treatment-emergent mood elevation	By 16 wk or before reaching criteria for durable recovery (up to 26 wk)	
No response	16 Wk reached without at least 1 wk of euthymia	16 wk	Receiving treatment without clinically significant improvement
Subject withdrawn owing to adverse effects without meeting criteria for first four outcomes	—	Any	
Other reasons for early termination	Treatment discontinued owing to noncompliance, loss to follow-up, or administrative or other reasons	Any	
Treatment-effectiveness response	50% Improvement from baseline SUM-D score* without meeting DSM-IV criteria for hypomania or mania	By 16 wk	Response rates modified as suggested in the effectiveness literature to more accurately capture beneficial response; used to facilitate comparison with data from Stanley Foundation Bipolar Network studies
Traditional efficacy equivalent	Durable recovery, transient remission, and treatment-emergent affective switch	Any	Used for comparison with data in the efficacy literature

* Scores range from 0 to 22; higher scores indicate more severe symptoms.

least 50% from their baseline scores and who did not meet the DSM-IV criteria for hypomania or mania.

STATISTICAL ANALYSIS

Summary statistics for continuous variables are presented as means with standard deviations or medians with interquartile ranges. Summary statistics for discrete variables are presented as percentages. Parametric and nonparametric analysis-of-variance methods and chi-square tests were used to compare the rates of baseline clinical and demographic characteristics, characteristics of the clinical course, side effects, and serious adverse events between the two groups.

Analyses included all subjects who were randomly assigned to a treatment group. Except where noted, analyses are based on the last observation carried forward. Logistic-regression models were used to determine whether there was an independent effect of treatment on outcome rates after adjustment for site and antidepressant preference (none, for paroxetine, or for bupropion). Given the observed rate of recovery of 27.3% among subjects receiving a mood stabilizer plus a matching placebo, the study had a statistical power of 80% to detect an absolute difference of 15% between the two groups in rates of recovery. A P value of 0.05 was considered to indicate statistical significance.

RESULTS

CHARACTERISTICS AND DISPOSITION OF SUBJECTS

Figure 1 shows the disposition of study subjects. There were no significant differences in the demographic or clinical characteristics of the two treatment groups at baseline (Table 2). Data on the course of treatment are listed in Table 3. There was no significant difference between the two groups in the mean time in treatment.

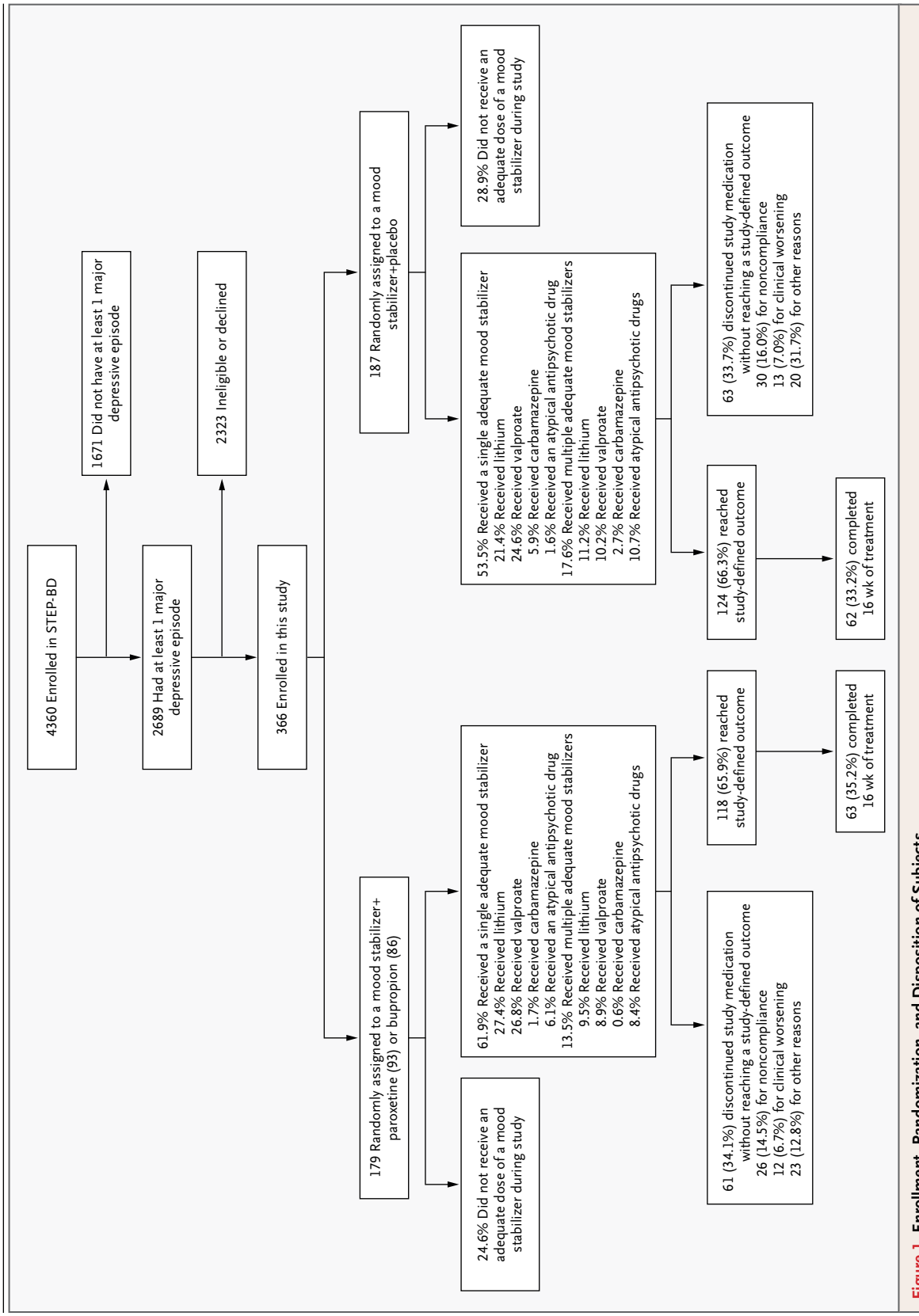

Figure 1. Enrollment, Randomization, and Disposition of Subjects.

At least one follow-up visit was completed by 163 of the 179 subjects (91.1%) in the group receiving a mood stabilizer plus an antidepressant and by 169 of the 187 subjects (90.4%) in the group receiving a mood stabilizer plus placebo. The percentages of subjects who reached a study-defined outcome, the percentages who discontinued treatment before week 16, and the rates of the causes of early termination were similar in the two groups. Clinical worsening was defined as the judgment by the clinician that depression contraindicated further participation in the study. STEP-BD denotes the Systematic Treatment Enhancement Program for Bipolar Disorder.

Table 2. Baseline Characteristics of Subjects, According to Treatment Group.*

Characteristic	Mood Stabilizer + Antidepressant (N = 179)	Mood Stablizer + Placebo (N = 187)	P Value
Site — no. (%)			0.97
Massachusetts General Hospital	40 (22.3)	40 (21.4)	
Baylor College	18 (10.1)	19 (10.2)	
Case Western Reserve University	31 (17.3)	32 (17.1)	
University of Oklahoma	13 (7.3)	16 (8.6)	
University of Pittsburgh	17 (9.5)	20 (10.7)	
University of Pennsylvania	14 (7.8)	10 (5.3)	
Other	46 (25.7)	50 (26.7)	
Male sex — no./total no. (%)	75/177 (42.4)	82/187 (43.9)	0.78
Age at study entry	40.0±11.4	40.0±11.9	0.87
No. with data	177	185	
Yr.	40.0±11.4	40.0±11.9	
Age at onset of bipolar symptoms	15.7±7.4	16.0±7.8	0.91
No. with data	172	179	
Yr.	15.7±7.4	16.0±7.8	
White race — no./total no. (%)†	163/179 (91.1)	168/187 (89.8)	0.69
Education level — no./total no. (%)			0.52
Some high school or high-school graduate	38/172 (22.1)	34/176 (19.3)	
Some education after high school	55/172 (32.0)	58/176 (33.0)	
Associate, technical, college, or postgraduate degree	79/172 (45.9)	84/176 (47.7)	
Annual income — no./total no. (%)			0.51
<$30,000	67/159 (42.1)	79/163 (48.5)	
$30,000–$74,999	59/159 (37.1)	55/163 (33.7)	
≥$75,000	33/159 (20.8)	29/163 (17.8)	
Marital status — no./total no. (%)			
Married	61/174 (35.1)	54/176 (30.7)	
Never married	61/174 (35.1)	68/176 (38.6)	
Divorced, widowed, or separated	52/174 (29.9)	54/176 (30.7)	
Bipolar-disorder subtype — no./total no. (%)			0.92
I	118/172 (68.6)	122/182 (67.0)	
II	54/172 (31.4)	60/182 (33.0)	
Anxiety disorder — no./total no. (%)			
Current	58/133 (43.6)	66/136 (48.5)	0.42
Lifetime	86/133 (64.7)	86/136 (63.2)	0.81

TREATMENT OUTCOMES

Treatment outcomes are defined in Table 1 and summarized in Table 4. There were no significant differences between the two groups in the percentage of subjects meeting the criteria for any effectiveness outcome. However, modest nonsignificant trends consistently favored treatment with a mood stabilizer plus a matching placebo over treatment with a mood stabilizer plus an adjunctive antidepressant. Similar percentages of subjects in each group did not have even a single week of euthymia over the first 16 weeks and were classified as having no response to an adequate course of treatment.

The rates of durable recovery were similar in the two groups among subjects with bipolar I dis-

Table 2. (Continued.)

Characteristic	Mood Stabilizer + Antidepressant (N = 179)	Mood Stablizer + Placebo (N = 187)	P Value
Substance abuse — no./total no. (%)			
Current	22/132 (16.7)	21/134 (15.7)	0.83
Lifetime	77/132 (58.3)	82/134 (61.2)	0.63
≥10 Previous manic episodes	108/177 (61.0)	124/185 (67.0)	0.23
≥10 Previous depressive episodes	120/174 (69.0)	125/185 (67.6)	0.95
History of rapid cycling — no./total no. (%)	44/162 (27.2)	53/168 (31.5)	0.38
History of treatment-emergent affective switch — no./total no. (%)	59/153 (38.6)	67/157 (42.7)	0.46
Participant in STEP-BD randomized psychosocial treatment study — no./total no. (%)	112/165 (67.9)	124/178 (69.7)	0.72
Clinical rating scores‡			
SUM-D	6.2±2.9	6.2±3.1	0.79
SUM-ME			0.96
No. with data	158	163	
Score	1.1±1.1	1.1±1.1	
MADRS			0.77
No. with data	145	151	
Score	24.5±10.0	24.0±9.4	
YMRS			0.46
No. with data	146	150	
Score	5.8±4.9	5.8±5.7	
GAF			0.70
No. with data	157	163	
Score	55.95±8.2	55.4±7.8	
CGI severity-of-illness subscale			0.38
No. with data	157	162	
Score	3.9±0.9	3.8±0.8	
Days in STEP-BD study before randomization	197.5±301.6	166.7±263.2	0.28

* Plus–minus values are means ±SD. STEP-BD denotes the Systematic Treatment Enhancement Program for Bipolar Disorder.
† Race was self-reported.
‡ The SUM-D and SUM-ME are the continuous symptom subscales for depression and mood elevation (mania), respectively, from the Clinical Monitoring Form; scores range from 0 to 22 and 0 to 16, respectively, with higher scores indicating more severe symptoms. Scores on the Montgomery–Asberg Depression Rating Scale (MADRS) and the Young Mania Rating Scale (YMRS) range from 0 to 60, with higher scores indicating greater severity of symptoms of depression and of mania, respectively. Scores on the Global Assessment of Functioning (GAF) scale range from 1 to 100, with higher scores indicating better functioning. Scores on the Clinical Global Impression Scale of Illness Severity (CGI) range from 1 to 7, with higher scores indicating greater severity of illness.

order. Among subjects with bipolar II disorder, there was a nonsignificant trend toward a better response in the patients receiving a mood stabilizer plus placebo than in those receiving a mood stabilizer plus an antidepressant. In the group receiving a mood stabilizer and an antidepressant, response rates did not differ significantly between subjects with bipolar I disorder (25.4%) and those with bipolar II disorder (20.4%).

Analysis of results that were adjusted for acceptance or rejection of enrollment into the STEP-BD randomized psychosocial treatment study showed no significant differences between the two groups (adjusted P=0.25 for the primary outcome). The augmentation of drug therapy with brief or intensive psychotherapy carried no significant benefit. For the subgroup of 130 subjects who rejected random assignment to a protocol-specified

Table 3. Clinical Course of Study Subjects.*

Characteristic	Mood Stabilizer + Antidepressant (N = 179)	Mood Stabilizer + Placebo (N = 187)	P Value
No. of study visits	7.0±4.4	7.2±4.8	0.84
Maximum dose — mg			
Paroxetine — median (IQR)	30 (20–40)	30 (20–40)	
Bupropion — median (IQR)	300 (150–300)	300 (150–375)	
Dose at exit — mg			
Paroxetine — median (IQR)	30 (20–40)	30 (20–40)	
Bupropion — median (IQR)	300 (150–300)	300 (150–338)	
Days receiving treatment	88.0±63.65	84.4±63.11	0.77
Any mood stabilizer at randomization — no. (%)	156 (87.2)	160 (85.6)	0.73
Adequate mood stabilizer at randomization — no./total no. (%)	135/177 (76.3)	133/184 (72.3)	0.39
Adequate mood stabilizer after randomization — no./total no. (%)	154/177 (87.0)	154/184 (83.7)	0.37
Marked or grossly disabling adverse event — no. of subjects (%)†	17 (9.5)	13 (7.0)	0.37
Tremor	1	1	
Clinically significant elevation of serum aspartate aminotransferase‡	10	0	
Diarrhea	0	1	
Headache	0	1	
Sexual dysfunction	4	2	
Abdominal pain	1	0	
A feeling of being "out of it"	0	1	
Agitation	2	0	
Rash	2	1	
Swelling	1	0	
Abnormal vision	0	1	
Light-headedness	1	0	
Nausea	2	0	
Irritability	0	1	
Insomnia	1	0	
Prone to being argumentative	1	0	
Anxiety	0	1	
Serious adverse events — no. of subjects (%)§	8 (4.5)	10 (5.3)	0.70
Medical hospitalization	4	0	
Medical illness	0	2	
Psychiatric hospitalization			
For depression	0	3	
For suicidal ideation	3	3	
Psychiatric hospitalization not related to depression, mania, mixed symptoms, or suicidal ideation	1	1	
Increased frequency of suicidal ideation without hospitalization	0	1	

* Plus–minus values are means ±SD. Adequate mood stabilizers were as follows, defined according to the dose (or serum level) of the drug: aripiprazole, ≥15 mg per day; carbamazepine, ≥600 mg per day (or ≥4 μg per milliliter); divalproex, ≥750 mg per day (or ≥45 μg per milliliter); lithium, ≥900 mg per day (or ≥0.4 mmol per liter); olanzapine, ≥10 mg per day; quetiapine, ≥300 mg per day; risperidone, ≥1 mg per day; ziprasidone, ≥80 mg per day. IQR denotes interquartile range.

† Adverse events were defined as unwanted effects, rated as mild, moderate (affecting function to some degree but not requiring reduction or discontinuation of dose), marked (substantially impairing the ability to function in social or occupational role or requiring reduction or discontinuation of dose), or grossly disabling (substantially impairing simple activities of daily living). The sum of the adverse events exceeds the number of subjects because some subjects had more than one adverse event.

‡ Clinically significant elevation of serum aspartate aminotransferase was defined as an elevation to more than twice the upper limit of the normal range or an elevation deemed by the clinician to warrant dose adjustment or discontinuation of medication.

§ Serious adverse events were defined as those that resulted in hospitalization, permanent disability, or death or required an intervention to prevent these outcomes.

N ENGL J MED 10.1056/NEJMoa064135

Table 4. Outcomes According to Treatment Group.*

Outcome	Mood Stabilizer + Antidepressant (N=179)	Mood Stabilizer + Placebo (N=187)	P Value
	number (percent)		
Transient remission	32 (17.9)	40 (21.4)	0.40
Durable recovery (primary outcome)	42 (23.5)	51 (27.3)	0.40†
Transient remission or durable recovery	74 (41.3)	91 (48.7)	0.23
Treatment-effectiveness response	58 (32.4)	71 (38.0)	0.27
Treatment-emergent affective switch	18 (10.1)	20 (10.7)	0.84
Discontinuation of study medication because of adverse event	22 (12.3)	17 (9.1)	0.32

* The study used an equipoise-stratified design, which allowed for the analysis of data stratified by the acceptance or rejection of enrollment into randomized psychosocial treatment study of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Outcomes are defined in Table 1.

† The P value for the main effect of treatment on the primary outcome of durable recovery, adjusted for acceptance or rejection of enrollment into randomized psychosocial treatment study of the STEP-BD, was 0.25.

psychotherapy, rates of recovery were 17.9% (12 of 67 subjects) in the group receiving a mood stabilizer plus an antidepressant and 30.2% (19 of 63 subjects) in the group receiving a mood stabilizer plus placebo (P=0.15); for the subgroup of 106 subjects who underwent brief psychoeducation, 20.0% (11 of 55 subjects) and 19.6% (10 of 51 subjects), respectively (P=0.99); and for the subgroup of 130 subjects who underwent intensive psychotherapy, 33.3% (19 of 57 subjects) and 30.1% (22 of 73 subjects), respectively (P=0.71). Furthermore, there was no significant interaction between the augmentation of drug therapy with psychotherapy and the type of psychosocial intervention used (P=0.28).

ADVERSE EVENTS

The numbers of subjects with adverse events of more than moderate severity and with serious adverse events are reported in Table 3. The rate of any individual adverse event did not differ significantly between the two groups, and similar percentages of subjects in each group discontinued treatment owing to adverse events. The rate of hospitalization for suicidal ideation was low and was not significantly different between the two groups. Less than 1% of subjects in either group attempted suicide. No patients died.

There was no significant difference in the rates of prospectively observed treatment-emergent mania, hypomania, or mixed episodes between the patients receiving a mood stabilizer plus an antidepressant (10.1%) and those receiving a mood stabilizer plus placebo (10.7%). Among subjects reporting treatment-emergent affective switch associated with one or more previous courses of treatment with antidepressants, response rates did not differ significantly between the group receiving a mood stabilizer plus an antidepressant and the group receiving a mood stabilizer plus placebo (13.6% and 25.4%, respectively; P=0.10), nor did the prospectively observed rates of treatment-emergent affective switch (10.2% and 17.9%, respectively; P=0.22). Among the subjects receiving a mood stabilizer plus an antidepressant, there were no significant differences in the rate of any primary or secondary outcome between subjects receiving bupropion and those receiving paroxetine.

DISCUSSION

This large, randomized, placebo-controlled effectiveness study found no evidence that treatment with a mood stabilizer and an antidepressant confers a benefit over treatment with a mood stabilizer alone. Rates of treatment-emergent mania or hypomania observed prospectively were similar among subjects receiving adjunctive antidepressants and those receiving placebo. Our data suggest that the short-term addition of bupropion or paroxetine to mood-stabilizer therapy does not increase the risk of cycling from depression to mania or hypomania. However, we did not study a "pure" placebo group (one in which no active psychotropic medication was administered) and hence cannot establish the effectiveness of treatment with a mood stabilizer alone.

There were several differences in the design of our study and that of previous studies. We primarily enrolled subjects who were already receiving clinical treatment at participating sites and who continued care with their usual provider. Our eligibility criteria permitted the entry of subjects with bipolar I or bipolar II disorder, including those with coexisting anxiety disorders, substance-abuse disorders, or psychotic symptoms, since epidemiologic evidence shows that most patients with bipolar disorder have such features.[20] We also allowed subjects to receive additional pharmacotherapy or psychotherapy. These differences may explain the disparity between our findings and those from the meta-analysis of efficacy studies by Gijsman et al.,[21] which found standard antidepressants to be efficacious in the treatment of bipolar depression.

Our study design also differed from that of most efficacy studies in that it featured equipoise-randomization strata. This design allowed the entry of subjects who preferred to avoid one of the standard antidepressants, by eliminating the possibility that the subjects would be randomly assigned to a treatment they did not want to receive. Finally, our a priori, clinically meaningful, primary outcome of durable recovery was met if subjects had euthymia for 8 consecutive weeks. In contrast, most short-term efficacy studies designate as the primary outcome change from the baseline score on symptom-severity scales at a single visit. Our results are therefore likely to be more in accord with the expectations of clinicians and patients in the general population for treatment effectiveness than are the results of previous efficacy studies.

Our study had several limitations. First, since antidepressants are not a homogeneous class, we cannot rule out the possibility that other antidepressant medications may be more efficacious or have a greater propensity to induce manic symptoms than our study medications. Nevertheless, bupropion and paroxetine are two of the most frequently recommended antidepressants for patients with bipolar disorder.[22] Some studies suggest that antidepressants vary in their tendency to cause a switch to mania or hypomania, even when used as adjuncts to mood-stabilizing treatments.[17,23,24] Notably, the largest of these studies — the double-blind comparison of bupropion, sertraline, and venlafaxine by the Stanley Foundation Bipolar Network — found no difference in efficacy among the treatments but did find a significantly higher rate of switch from depression to mania or hypomania among subjects receiving venlafaxine than among those receiving bupropion or sertraline.[9,24] Therefore, although neither paroxetine nor bupropion was associated with an increased rate of treatment-emergent affective switch in our study, other antidepressants may be. Our results are, however, largely in agreement with those from studies that associate selective serotonin-reuptake inhibitors and bupropion with lower rates of treatment-emergent affective switch than venlafaxine or desipramine.[17,23]

Second, our efficacy and safety findings are based on a relatively brief period of observation. The primary outcome of 8 consecutive weeks of euthymia, however, reflects a considerably longer period than do the cross-sectional outcomes (response or remission) used in typical efficacy studies. Although an 8-week period of recovery may be too brief to be clinically meaningful for patients, an 8-week interval of wellness may be a better predictor of long-term outcome than are scores on cross-sectional rating scales. Effectiveness outcomes such as those used in our study may be more applicable to clinical practice than are short-term cross-sectional outcomes, since the apparent benefit based on cross-sectional outcomes may not be persistent and since nearly all traditional efficacy trials define outcomes on the basis of improvement in depression-rating scores without correction for rates of treatment-emergent affective switch. Results from traditional efficacy studies can thereby misclassify patients with emergent hypomania or mania as having had a response. The Stanley Foundation Bipolar Network, using outcome criteria corrected for rates of treatment-emergent affective switch, reported that 33.3% of patients with bipolar depression had a response to treatment with bupropion, 41.4% had a response to sertraline, and 35.6% had a response to venlafaxine[24]; these response rates are similar to the treatment-effectiveness response rates reported here.

Third, many of our study subjects received some form of psychosocial intervention. Although the efficacy of psychosocial therapies has not been established for patients with acute bipolar depression,[25,26] it is possible that the adjunctive use of psychosocial interventions limits the generalizability of our results or reduced our ability to detect the effects of antidepressant therapy. Psy-

chosocial intervention did not appear to affect the two study groups differently. The two groups had similar percentages of subjects who received psychosocial interventions, and similar response rates were found in the subgroups receiving any form of psychosocial intervention and in the subgroup that declined psychosocial treatment. Results of a longer-term STEP-BD study do provide support for use of the psychosocial interventions used in our study.[18]

Fourth, some of our findings rely on last-observation-carried-forward analyses. Such analyses generally involve the imputation of data, which raises concern about the degree to which incomplete follow-up influenced the results. However, data imputation was not required for analysis of the primary outcome (durable recovery) or of the majority of secondary outcomes reported in our study. These categorical outcomes represent subjects who actually reached a study-defined outcome. Some data for the change in SUM-D and SUM-ME scores were imputed, but this is unlikely to have influenced our outcomes, as it was required for only about one third of the subjects in each group.

Fifth, patients who had recently had a manic episode were likely to be underrepresented in our study. Clinicians caring for these potential subjects might have judged them to be at high risk for a switch from depression to mania or hypomania and therefore might have avoided enrolling them into our double-blind study that exposed subjects to a standard antidepressant. Thus, our results are likely to be applicable only to those patients with bipolar depression who are considered appropriate candidates for treatment with standard antidepressants.

In summary, for the treatment of bipolar depression, we found that mood-stabilizing monotherapy provides as much benefit as treatment with mood stabilizers combined with a standard antidepressant. There was no significant difference in the adverse effects, including switch to mania, between patients who received adjunctive antidepressants and those that did not. Further research examining the efficacy of different mood stabilizers for bipolar depression may be useful.

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REFERENCES

1. Murray CJ, Lopez AD, Jamison DT. The global burden of disease in 1990: summary results, sensitivity analysis and future directions. Bull World Health Organ 1994;72:495-509.

2. Kessler RC, Demler O, Frank RG, et al. Prevalence and treatment of mental disorders, 1990 to 2003. N Engl J Med 2005; 352:2515-23.

3. Simon GE, Unutzer J. Health care utilization and costs among patients treated for bipolar disorder in an insured population. Psychiatr Serv 1999;50:1303-8.

4. Judd LL, Akiskal HS, Schettler PJ, et al. The long-term natural history of the weekly symptomatic status of bipolar I disorder. Arch Gen Psychiatry 2002;59: 530-7.

5. Post RM, Denicoff KD, Leverich GS, et al. Morbidity in 258 bipolar outpatients followed for 1 year with daily prospective ratings on the NIMH life chart method. J Clin Psychiatry 2003;64:680-90, 738-9.

6. Perlis RH, Ostacher MJ, Patel JK, et al. Predictors of recurrence in bipolar disorder: primary outcomes from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2006;163:217-24.

7. Goodwin GM. Evidence-based guidelines for treating bipolar disorder: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2003;17:147, 149-73.

8. Suppes T, Dennehy EB, Hirschfeld RM, et al. The Texas Implementation of Medication Algorithms: update to the algorithms for treatment of bipolar I disorder. J Clin Psychiatry 2005;66:870-86.

9. Leverich GS, Altshuler LL, Frye MA, et al. Risk of switch in mood polarity to hypomania or mania in patients with bipolar depression during acute and continuation trials of venlafaxine, sertraline, and bupropion as adjuncts to mood stabilizers. Am J Psychiatry 2006;163:232-9.

10. Ghaemi SN, Hsu DJ, Thase ME, et al. Pharmacological treatment patterns at study entry for the first 500 STEP-BD participants. Psychiatr Serv 2006;57:660-5.

11. Nemeroff CB, Evans DL, Gyulai L, et al. Double-blind, placebo-controlled comparison of imipramine and paroxetine in the treatment of bipolar depression. Am J Psychiatry 2001;158:906-12.

12. Tohen M, Vieta E, Calabrese J, et al. Efficacy of olanzapine and olanzapine-fluoxetine combination in the treatment of bipolar I depression. Arch Gen Psychiatry 2003;60:1079-88. [Erratum, Arch Gen Psychiatry 2004;61:176.]

13. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Biol Psychiatry 2003;53:1028-42.

14. Spitzer RL, Williams JB, Gibbon M, First MB. The Structured Clinical Interview for DSM-III-R (SCID). I. History, rationale, and description. Arch Gen Psychiatry 1992;49:624-9.

15. Sheehan DV, Lecrubier Y, Sheehan KH, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59: Suppl 20:22-57.

16. Goldberg JF, Allen MH, Miklowitz DA, et al. Suicidal ideation and pharmacotherapy among STEP-BD patients. Psychiatr Serv 2005;56:1534-40.

17. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391-3.

18. Miklowitz DJ, Otto MW, Frank E, et al. Psychosocial treatments for bipolar depression: a 1-year randomized trial from the Systematic Treatment Enhancement Program. Arch Gen Psychiatry (in press).

19. Sachs GS, Guille C, McMurrich SL. A Clinical Monitoring Form for mood disorders. Bipolar Disord 2002;4:323-7.

20. Kessler RC, Chiu WT, Demler O, Merikangas KR, Walters EE. Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005;62:617-27. [Erratum, Arch Gen Psychiatry 2005:62:709.]

21. Gijsman HJ, Geddes JR, Rendell JM, Nolen WA, Goodwin GM. Antidepressants for bipolar depression: a systematic review of randomized, controlled trials. Am J Psychiatry 2004;161:1537-47.

22. American Psychiatric Association. Practice guideline for the treatment of patients with bipolar disorder (revision). Am J Psychiatry 2002;159:Suppl:1-50.

23. Vieta E, Martinez-Aran A, Goikolea JM, et al. A randomized trial comparing paroxetine and venlafaxine in the treatment of bipolar depressed patients taking mood stabilizers. J Clin Psychiatry 2002;63:508-12.

24. Post RM, Altshuler LL, Leverich GS, et al. Mood switch in bipolar depression: comparison of adjunctive venlafaxine, bupropion and sertraline. Br J Psychiatry 2006;189:124-31. [Erratum, Br J Psychiatry 2006;189:569.]

25. Frank E, Swartz HA, Mallinger AG, Thase ME, Weaver EV, Kupfer DJ. Adjunctive psychotherapy for bipolar disorder: effects of changing treatment modality. J Abnorm Psychol 1999;108:579-87.

26. Scott J, Paykel E, Morriss R, et al. Cognitive-behavioural therapy for severe and recurrent bipolar disorders: randomised controlled trial. Br J Psychiatry 2006;188:313-20.

Attachment I

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- About ORI
- Assurance
- Conferences
- Forensic Tools
- Handling Misconduct
- International
- Policies / Regulations
- Publications
- RCR Education
- Research
- RIOs

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Handling Misconduct - Whistleblowers

ORI Guidelines for Institutions and Whistleblowers: Responding to Possible Retaliation Against Whistleblowers in Extramural Research

(November 20, 1995)

I. INTRODUCTION

The Office of Research Integrity (ORI), Department of Health and Human Services (DHHS), strongly believes in the importance of protecting whistleblowers who make good faith allegations of scientific misconduct to ORI or appropriate institutional authorities. In particular, ORI is committed to protecting good faith whistleblowers from retaliation by covered institutions and their members.

By regulation, each extramural entity that applies for a biomedical or behavioral research, research-training, or research-related grant or cooperative agreement under the Public Health Service (PHS) Act must establish policies and procedures that provide for "undertaking diligent efforts to protect the positions and reputations of those persons who, in good faith, make allegations." 42 C.F.R. Part 50.103(d)(13).

Although the regulation does not provide specific direction on how to protect whistleblowers, ORI has determined that adherence to the policies and procedures set forth in these Guidelines is one method of satisfying the requirements of the regulation. ORI will recognize an institution's substantial conformity with these Guidelines as meeting the whistleblower protection requirement of 42 C.F.R. Part 50.103(d)(13). Specifically, each institution which substantially adheres to Sections IV and V of these Guidelines in responding to whistleblower retaliation complaints will be considered in compliance with the regulatory whistleblower protection requirement for resolution of retaliation complaints. However, institutions are free to disregard these Guidelines and adopt other procedures that conform to the regulatory requirement.

If an institution elects to adopt these Guidelines, it must abide by each provision that uses the operative word "shall." On the other hand, provisions which employ the words "should" or "may" are merely practical suggestions. An institution will not be out of conformity with the Guidelines if it fails to carry out these recommendations. Rather, an institution may substitute for these suggested provisions alternative procedures that are consistent with the mandatory provisions of these Guidelines and the regulatory whistleblower protection provisions.

In addition to the requirements of 42 C.F.R. Part 50.103(d)(13), ORI encourages covered institutions to adopt policies and procedures that conform to PHS Act Part 493(e), a whistleblower protection statute enacted by Part 163 of the National Institutes of Health Revitalization Act of 1993, although Part 493 has not been implemented by regulation at the time of issuance of these Guidelines. Besides protecting good faith allegations of scientific misconduct, PHS Act Part 493(e) mandates the protection of whistleblowers for (1) good faith allegations of an inadequate institutional response to scientific misconduct allegations and (2) good faith cooperation with investigations of such allegations. The statute covers allegations of misconduct which involve research or research related grants, contracts or cooperative agreements under the PHS Act.

ORI also encourages institutions to adopt principles consistent with the Whistleblower Bill of Rights (Appendix A) recommended by the Commission on Research Integrity and to foster institutional commitment to those principles. The specific principles of the Whistleblower Bill of Rights are as follows:

(1) whistleblowers are free to disclose lawfully whatever information supports a reasonable belief of research misconduct as it is defined by PHS policy,

(2) institutions have a duty not to tolerate or engage in retaliation against good-faith whistleblowers,

(3) institutions have a duty to provide fair and objective procedures for examining and resolving complaints, disputes and allegations of research misconduct,

(4) institutions have a duty to follow procedures that are not tainted by partiality arising from personal or institutional conflict of interest or other sources of bias,

(5) institutions have a duty to elicit and evaluate fully and objectively information about concerns raised by whistleblower,

(6) institutions have a duty to handle cases involving alleged research misconduct as expeditiously as possible without compromising responsible resolutions, and

(7) at the conclusion of proceedings, institutions have a responsibility to credit promptly, in public or private as appropriate, those whose allegations are substantiated.

These Guidelines are consistent with the rights and responsibilities enumerated in the Whistleblower Bill of Rights.

Handling Misconduct

- Introduction
- Technical Assistance
- Complainant
- Respondents
- Allegations
- Preliminary Assessment
- Inquiries
- Investigations
- Institutional Decision
- ORI Oversight Review
- PHS/HHS Decision
- Hearings
- Administrative Actions
- Case Summaries
- Legal Concerns
- Forensic Tools

While compliance with these Guidelines will satisfy the existing regulatory requirements at 42 C.F.R. Part 50.103 (d)(13), this publication does not bind the Department in any way as to the substantive provisions of the forthcoming new regulation implementing the whistleblower protection statute, PHS Act Part 493(e).

II. PURPOSE

The purpose of these Guidelines is to set forth ORI's suggested approach for handling whistleblower retaliation cases which arise at covered institutions. Substantial adherence to the Guidelines in each whistleblower case affords a "safe harbor" in which conforming institutions will be deemed in compliance with Part 50.103(d)(13) of the scientific misconduct regulation. For those institutions which adopt alternative procedures to comply with the regulation, ORI may review those cases which do not abide by these Guidelines to determine whether an institution has taken diligent efforts to protect the positions and reputations of good faith whistleblowers.

These Guidelines also provide information to whistleblowers on an appropriate method of submitting retaliation complaints and subsequent procedures for resolving the complaints. ORI encourages whistleblowers to refer institutions to these Guidelines when making specific complaints of retaliation.

These Guidelines apply to all instances of possible retaliation against whistleblowers whose allegation of scientific misconduct is covered by 42 C.F.R. Part 50, Subpart A.

III. DEFINITIONS

"**Adverse action**" means any action taken by a covered institution or its members which negatively affects the terms or conditions of the whistleblower's status at the institution, including but not limited to his or her employment, academic matriculation, awarding of degree, or institutional relationship established by grant, contract or cooperative agreement.

"**Allegation**" means any disclosure, whether by written or oral statement, or any other communication, to an institutional, a Department of Justice (DOJ), or a DHHS official who receives the allegation while acting in their official capacity, that a covered institution or member thereof has engaged in scientific misconduct. Allegations made to any of the above officials may be in conjunction with communications to Congress (1).

"**Arbitration**" means the process described in this Part through which an unresolved dispute regarding whistleblower retaliation is submitted to an arbitrator for a final and binding decision.

"**Arbitrator**" means one or more impartial persons selected according to the rules of a designated arbitration association who shall hear and decide whistleblower retaliation complaints under this Part.

"**Covered institution**" means any entity, whether individual or corporate, which applies for or receives funds under a research, research-training, or research-related grant or cooperative agreement under the PHS Act.

"**Deciding official**" means the official designated by the administrative head of a covered institution to make a final institutional determination as to whether retaliation occurred.

"**Good faith allegation**" means an allegation of scientific misconduct made with a belief in the truth of the allegation which a reasonable person in the whistleblower's position could hold based upon the facts. An allegation is not in good faith if made with reckless disregard for or willful ignorance of facts that would disprove the allegation.

"**Institutional member, or member**" means a person who is employed by, affiliated with under a contract or agreement, or under the control of a covered institution. Institutional members include but are not limited to administrative, teaching and support staff, researchers, clinicians, technicians, fellows, students, and contractors and their employees.

"**Office of Research Integrity (ORI)**" means the office to which the Secretary has delegated responsibility for addressing scientific misconduct issues related to PHS activities, including the protection of good faith whistleblowers.

"**Responsible official**" means the official designated by and reporting to the administrative head of a covered institution to establish and implement the institution's whistleblower policies.

"**Retaliation**" means any adverse action or credible threat of an adverse action taken by a covered institution, or member thereof, in response to a whistleblower's good faith allegation of scientific misconduct. It does not include an institution's decision to investigate a good faith allegation of scientific misconduct.

"**Scientific misconduct**" means fabrication, falsification, plagiarism, or other practices that seriously deviate from those that are commonly accepted within the scientific community for proposing, conducting, or reporting research. It does not include honest error or honest differences in interpretations or judgments of data.

"**Whistleblower**" means an individual who makes an allegation or demonstrates an intent to make an allegation (or what is perceived to be an allegation) while a member of the institution at which the alleged scientific misconduct occurred.

IV. PROCESSING WHISTLEBLOWER RETALIATION COMPLAINTS

A. Responsible Official

1. Covered institutions shall designate a "responsible official" to establish and implement the institution's whistleblower policies according to 42 C.F.R. Part 50.103(d)(13) and these Guidelines. The responsible official also serves as a liaison between the

institution and ORI for transmitting such information as ORI may require.

2. The responsible official shall be free of any real or apparent conflicts of interest in any particular case.

3. If involvement of the responsible official in a particular case creates a real or apparent conflict of interest with the institution's obligation to protect good faith whistleblowers, and the conflict cannot be satisfactorily resolved for that case, the administrative head of the institution shall appoint a substitute responsible official who has no conflict of interest.

B. Notice of Institutional Policy

The institution shall provide to all its members notice of its whistleblower policies and these Guidelines with Appendices. The notice shall include the requirement set forth below regarding a whistleblower's deadline for filing a retaliation complaint. The institution's policies and these Guidelines shall be either disseminated or be publicized and made readily available to all institutional members.

C. Filing Complaints

1. A whistleblower who wishes to receive the procedural protections described by these Guidelines shall file his or her retaliation complaint with the responsible official at the appropriate institution within 180 days (2) from the date the whistleblower became aware or should have become aware of the alleged adverse action. Covered institutions shall review and resolve all whistleblower retaliation complaints and should do so within 180 days after receipt of the complaint. If the whistleblower fails to receive an institutional response to the complaint in accordance with these Guidelines within ten (10) working days (3), the whistleblower may file the retaliation complaint directly with ORI at the following address:

Office of Research Integrity
Division of Investigative Oversight
1101 Wootton Parkway, Suite 750
Rockville, MD 20852
Telephone: (240) 443-8800
Fax: (301) 594-0043

ORI will forward such complaints to the institution's responsible official for appropriate action.

2. In addition to prospective complaints, institutions may apply these Guidelines to complaints of retaliation made prior to the effective date of the institution's adoption of these Guidelines.

3. The retaliation complaint must include a description of the whistleblower's scientific misconduct allegation and the asserted adverse action, or threat thereof, against the whistleblower, by the institution or its members in response to the allegation. If the retaliation complaint is incomplete, the responsible official shall describe to the whistleblower what additional information is needed in order to meet the minimum requirements of a complaint under this Part.

D. Responding to Complaints

1. Upon receipt of a whistleblower retaliation complaint, the responsible official shall notify the whistleblower of receipt within ten (10) working days (4) after receipt. The notice shall also inform the whistleblower of which process under Section V of the Guidelines the institution proposes to follow in resolving the retaliation complaint and the necessary actions by the whistleblower required under that process. The notice shall also notify the whistleblower of his or her choice of responses listed below.

2. The whistleblower may raise any concerns about the proposed process with the responsible official and the institution may modify the process in response to the whistleblower's concerns.

3. The whistleblower has five working days from the date of receipt of the initial notification in Part 1 above to:

a. accept the proposed process, although the whistleblower may also submit documentation for the official record about any concerns he or she may have about the proposed process; or

b. not accept the proposed process. If the whistleblower rejects the proposed process, he or she may pursue other remedies as provided by law.

4. If the whistleblower does not accept the proposed process, the institution may, but is not required to, propose the alternative option under Section V of the Guidelines.

5. The institution shall notify ORI of any whistleblower retaliation complaint it receives within ten (10) working days (5) after receipt of the complaint.

E. Interim Protections

1. At any time before the merits of a whistleblower retaliation complaint have been fully resolved, the whistleblower may submit a written request to the responsible official to take interim actions to protect the whistleblower against an existing adverse action or credible threat of an adverse action by the institution or member.

2. Based on the available evidence, the responsible official shall make a determination of whether to provide interim protections and shall advise the whistleblower of his or her decision in writing. Documentation underlying the decision whether to provide interim protections shall become part of the record of the complaint. When the whistleblower retaliation complaint is fully

resolved, any temporary measure taken to protect the whistleblower shall be discontinued or replaced with permanent remedies.

V. RESOLUTION OF COMPLAINTS

1. For each whistleblower retaliation complaint received, a covered institution shall adhere to one of the two alternative processes for resolving the whistleblower retaliation complaint, or settle the complaint, as described below.

2. Whichever process is elected shall be implemented in a timely fashion. The process should be completed within 180 days of the date the complaint is filed, unless the whistleblower agrees to an extension of time. The institution shall promptly report the final outcome of either process or any settlement to ORI.

3. If the whistleblower declines the institution's proposed process according to these Guidelines, he or she may pursue any other legal rights available to the whistleblower for resolution of the retaliation complaint. However, ORI will deem the institution to have met its obligation under 42 C.F.R. Part 50.103(d)(13) and will not pursue the whistleblower complaint further.

Option A: Institutional Investigation

1. If the institution elects Option A, the institution shall conduct an investigation of the whistleblower retaliation complaint according to these Guidelines and implement appropriate administrative remedies consistent with the investigation's finding and institutional decision thereon.

2. An investigation of whistleblower retaliation shall be timely, objective, thorough, and competent. The investigation should be conducted by a panel of at least three (3) individuals appointed by the responsible official. The members of the investigation panel, who may be from outside the institution, shall have no personal or professional relationship or other conflict of interest with the whistleblower or the alleged individual retaliator(s), and shall be qualified to conduct a thorough and competent investigation.

3. The investigation shall include the collection and examination of all relevant evidence, including interviews with the whistleblower, the alleged retaliator(s), and any other individual who can provide relevant and material information regarding the claimed retaliation.

4. The institution shall fully cooperate with the investigation and use all available administrative means to secure testimony, documents, and other materials relevant to the investigation.

5. The confidentiality of all participants in the investigation shall be maintained to the maximum extent possible throughout the investigation.

6. The Panel members shall evaluate and respond objectively to any concerns raised by the whistleblower about the process, including concerns regarding the selection of the deciding official, responsible official and specific panel members, which are raised prior to resolution of the complaint.

7. The conclusions of the investigation shall be documented in a written report and made available to the whistleblower. The report shall include findings of fact, a list of witnesses interviewed, an analysis of the evidence, and a detailed description of the investigative process.

8. The deciding official shall make a final institutional determination as to whether retaliation occurred. This decision shall be based on the report, the record of the investigation, and a preponderance of evidence standard.

9. If there is a determination that retaliation has occurred, the deciding official shall determine what remedies are appropriate to satisfy the institution's regulatory obligation to protect whistleblowers. The deciding official shall, in consultation with the whistleblower, take measures to protect or restore the whistleblower's position and reputation, including making any public or private statements, as appropriate. In addition, the deciding official may provide protection against further retaliation by monitoring or disciplining the retaliator.

10. The institution shall promptly notify ORI of its conclusions and remedies, if any, and forward the underlying investigation report to ORI.

11. The ORI will review the institutional report to determine whether the institution has substantially followed the process described herein. If the institution has substantially conformed to the process, ORI will not review the merits of the institutional determination under Paragraphs 8 and 9.

12. Institutional compliance with Option A does not bar the whistleblower from seeking redress against the institution's decision under Paragraph 8 and 9, under State law, institutional procedure, policy or agreement, or as otherwise provided by law.

Option B: Arbitration

1. If the institution elects Option B, the institution shall offer the whistleblower the opportunity to submit the retaliation dispute to binding arbitration. The parties shall sign a written agreement that the retaliation dispute will be decided by final and binding arbitration, identifying the person who shall conduct the arbitration.

2. The arbitration agreement shall specify that the institution and the whistleblower abrogate all other rights under Federal, State and local law, and other institutional policies or employment agreements pertinent to the resolution of the whistleblower retaliation complaint, other than enforcement of the arbitration award. However, the parties may enter into any legally enforceable settlement agreement before a final arbitration award is made. A sample arbitration agreement is attached at

Appendix B.

3. Any retaliation complaint submitted to arbitration shall be arbitrated according to the rules and procedures of the presiding arbitrator and designated arbitration association.

4. An arbitration under these Guidelines shall be conducted by an arbitrator who has no personal or professional relationship or conflict of interest with the whistleblower, the institution, the alleged retaliator(s), or any person who is the subject of the underlying scientific misconduct allegation. The institution and the whistleblower shall agree on the choice of arbitrator. The arbitration should be facilitated by the American Arbitration Association or any other recognized non-profit arbitration association.

5. The institution and the whistleblower shall share equally the administrative costs of the arbitration. Each party is responsible for the cost of presenting its own case.

6. The arbitration agreement shall specify that the arbitrator shall require the institution to compensate the whistleblower for part or all of his or her arbitration costs, including attorney fees, if the arbitrator finds that the institution, or its members, retaliated against the whistleblower.

7. The arbitration agreement shall also specify that the arbitrator shall require the whistleblower to compensate the institution for part or all of any filing fees and arbitrator's costs if the arbitrator finds that the whistleblower's allegation of scientific misconduct was not made in good faith. If an institution seeks compensation on this basis, it shall make a preliminary motion to dismiss the retaliation complaint prior to commencement of a hearing. The arbitrator shall, if possible, make a threshold decision on the question of good faith based on written submissions prior to commencement of a hearing on the merits of the retaliation dispute. The institution has the burden of proving by a preponderance of the evidence that the allegation of scientific misconduct was not made in good faith.

8. The arbitration agreement shall specify a preponderance of the evidence standard in determining whether retaliation occurred or any other standard mutually agreed to by the parties.

9. The arbitration agreement shall state that the arbitrator's award is final and binding on all parties, and enforceable as provided by law.

10. If the arbitrator finds that the institution, or its members, retaliated against the whistleblower, the arbitrator may order any relief necessary to make the whistleblower whole for the direct or indirect consequences of retaliation, including protection against further retaliation through imposing a system to monitor or discipline the retaliator. The institution shall abide by the arbitrator's final award and shall implement any additional administrative actions it determines is necessary to correct the retaliation.

11. The institution shall promptly forward a copy of the final arbitration award to ORI.

C. Settlement

In lieu of the two options described above, an institution and whistleblower may, at any time after the retaliation complaint is made, enter into any binding settlement agreement which finally resolves the retaliation complaint. If both parties agree, the responsible official shall facilitate negotiation of such settlements. If such an agreement is reached, the institution and the whistleblower shall sign a statement indicating that the retaliation complaint has been resolved. The institution shall within 30 days send a copy of the signed statement to ORI. ORI does not require a copy of the actual terms of the settlement. The settlement may not restrict the whistleblower from cooperating with any investigation of an allegation covered by 42 C.F.R. Part 50, Subpart A. ORI shall consider a settlement meeting these requirements as fulfilling the institution's regulatory obligation under 42 C.F.R. Part 50.103(d)(13).

VI. INSTITUTIONAL COMPLIANCE

At any time ORI may review a covered institution's compliance with 42 C.F.R. Part 50.103(d)(13) and these Guidelines to the extent that the institution relies on these Guidelines for regulatory compliance. Covered institutions and their members shall cooperate with any such review and provide ORI access to all relevant records. If a covered institution's procedures and implementation thereof substantially conforms to Sections IV and V above, it shall be deemed to have met its whistleblower protection obligation under 42 C.F.R. Part 50.103(d)(13).

Footnotes:

(1) Communications to Congress must be made in a way that affords "affected individual(s) confidential treatment to the maximum extent possible" consistent with 42 C.F.R. 50.103 (d)(3).
(2) The institution may establish a longer period of time.
(3)The institution may establish a shorter period of time.
(4)The institution may establish a shorter period of time consistent with footnote 2.
(5)The institution may establish a shorter period of time.

U.S. Department of Health and Human Services
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Attachment J

To: Dr. Karl Rickels
From: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
Subject: SKB Bipolar study
Cc: dlevans@mail.med.upenn.edu
Bcc:
Attached:

Karl,

It has been about 5 or 6 weeks since I brought to your attention the troubling issue of investigator contribution and authorship on manuscripts from the SKB BP I study. You will recall that at least one manuscript from this study is in press to the Am J Psych, and other manuscripts may also have been submitted to other journals. Again, it is my feeling that as a major investigator in this nineteen-site study, I should have been provided with data for review and consideration for authorship on these manuscripts. As we discussed it was agreed upon in 1995 by you, me and Dr. Guylai that if I would have a major input into this study at the Penn site and serve as a major contributor to the study, then I should have input into data analysis and authorship. In our discussion several weeks ago you indicated your recollection of this agreement, and your understanding of the situation and its potential ramifications and that you would look into the matter. As I have not heard from you regarding this potentially troubling situation I thought that I would take the liberty of reminding you of it. As one of the articles is no doubt close to publication, I felt it necessary to speak with Dr. Evans. I did this several weeks ago regarding the situation and he indicated to me that he would speak to you about it.

As I previously indicated to you it is not my intention to put you in a difficult situation, and that if you feel uncomfortable helping out in this matter, please let me know so that I can take up the issue with others at the University and/or the American Journal of Psychiatry.

I look forward to hearing from you at your earliest convenience, and I thank you for your assistance in this matter.

Regards,
Jay

Attachment K

UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER
University of Pennsylvania School of Medicine
Hospital of the University of Pennsylvania

Karl Rickels, M.D.
Stuart and Emily B. H. Mudd Professor
Chief, Mood and Anxiety Disorders Section
Department of Psychiatry

April 3, 2001

D Jay Amsterdam, M.D.
Department Psychiatry
University of Pennsylvania
3600 Market Street, 8th Floor
Philadelphia, PA 19104-2649

RE: Bipolar Paper Authorship

Dear Jay,

After you talked to Dwight Evans about the bipolar paper authorship problem, he called me to look into this matter. I did so and on March 29, 2001, I emailed Dwight what I could learn. I reported to him on the following points:

1. Dr. Gyulai was contacted to be the PI for the Penn Site in 1994.

2. In 1995, I suggested that Dr. Gyulai ask Dr. Amsterdam whether he could help him with the project as Dr. Gyulai had problems enrolling patients. Dr. Amsterdam at that time was short in research funds and thus his participation could benefit both Dr. Gyulai and Dr. Amsterdam. Dr. Gyulai would enroll more patients and Dr. Amsterdam would receive more income for his unit. At this time, Dr. Amsterdam became a co-investigator.

3. Penn enrolled 19 patients into the randomized part of the study, with Dr. Amsterdam enrolling 12 patients and Dr. Gyulai enrolling 7 patients.

4. On April 8, 1997, Dr. Gyulai was asked by Grace Johnson of STI to serve as first author of the paper and to review and comment on the enclosed draft #2. On May 14, 1997, Ms. Johnson forwarded a diskette containing draft #2. On December 3, 1997, Dr. Gyulai mailed to Dr. Gergel a revised draft of the paper.

5. As you know, at some later date, SKB decided to replace Dr. Gyulai with Charlie Nemeroff as first author.

6. All participants in the study, including Dr. Amsterdam, are acknowledged in the paper.

7. However, apparently these participants never had a chance to review or even just see the manuscript.

3535 Market Street • Suite 670 • Philadelphia, PA 19104-3309 • Tel: 215-746-6417 • Fax: 215-349-5173 • Email: krickels@mail.med.upenn.edu

8. Probably one of the reasons Dr. Gyulai did not communicate with Dr. Amsterdam regarding the paper are the existing interpersonal conflicts between Dr. Gyulai and Dr. Amsterdam.

9. Dr. Gyulai recently communicated with SKB and requested permission to write a second paper as first author based on the same data. He proposed that this paper deal with an analysis of all HAM-D subscales and a 2 X 2 factorial analysis (2 treatment x high vs low Lithium levels). Dr. Gyulai expressed the hope that Dr. Amsterdam would be allowed by SKB to join him as one of several authors in this second publication.

10. Dr. Gyulai told me, but I have no independent confirmation, that he suggested to SKB that Dr. Amsterdam should be considered as an author for the first paper. This was turned down on the reasonable basis that only one author per site could be considered. In fact, several sites were not even considered for authorship.

I thought you might be interested in what I have learned.

Sincerely,

Karl

Karl Rickels, M.D.

KR:tch

Attachment L

UNIVERSITY OF
PENNSYLVANIA
MEDICAL CENTER

University of Pennsylvania School of Medicine
Hospital of the University of Pennsylvania

Laszlo Gyulai, M.D.
Associate Professor
Director, Bipolar Disorders Program

Department of Psychiatry
Mood and Anxiety Disorders Section

Jay D. Amsterdam, M.D.
Professor, Director,
Depression Research Unit,
Mood and Anxiety Disorders Section
Department of Psychiatry
University of Pennsylvania

7/5/01

Dear Jay,

I regret that there appears to be some misunderstanding about the publication of the data of the SKB PAR- 29060/352 study, which was conducted between 1994 and 1996 and I sincerely apologize for it. I understand that you feel that I took your data collected in this study and that I was unfairly one of the authors of the paper from the project, which appeared in the Am. J. Psychiatry.

I was the primary investigator of the Penn site and, as you know, I worked on early drafts of the paper. I did not determine authorship, and as you know, the paper was taken away from me as first author during the writing process. However, I regret that I did not discuss the issue of authorship with you. I agree with you that SKB should have circulated the paper to all participants. I only saw the final draft shortly before it was submitted when only minor changes could be done.

I hope that this clarifies some of the misunderstandings and makes it possible for us to work in a collaborative fashion. I am truly sorry about the whole matter and would be happy to personally meet with you and discuss these issues as colleague to colleague.

I remain sincerely yours,

Laszlo Gyulai, M.D.

cc: Dr. Dwight L. Evans
Dr. Karl Rickels

3535 Market Street • Suite 670 • Philadelphia, PA 19104-3309 • Tel: 215-746-6415 • Fax: 215-898-0509

Attachment M

X-Sender: psych@mail.med.upenn.edu
X-Mailer: QUALCOMM Windows Eudora Light Version 3.0.3 (32)
Date: Thu, 22 Mar 2001 04:31:18 -0500
To: jamsterd@mail.med.upenn.edu
From: "Dr. Dwight L. Evans, MD" <psych@mail.med.upenn.edu>
Subject: SKB Study
Cc: krickels@mail.med.upenn.edu

Dear Jay,

I have discussed the SKB study at length with Karl Rickels. He will review and look into the entire matter as it relates to the work that you did here at Penn. Once this is accomplished, I trust there will be an equitable outcome.

Dwight

Dwight L. Evans, MD
Ruth Meltzer Professor and Chairman
Department of Psychiatry
University of Pennsylvania Health System
3 Blockley Hall
Philadelphia, PA 19104
215-662-2818
215-662-6911 Fax
Email: psych@mail.med.upenn.edu

Attachment N

To: "Dr. Dwight L. Evans, MD" <psych@mail.med.upenn.edu>
From: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
Subject: SKB study publication
Cc:
Bcc:
Attached:

Hi Dwight,

To date there has been only "radio silence" regarding the matter of the Am J Psychiatry publication. Am I to assume that it is okay in this department for a junior faculty member to abscond with data from a full professor and publish it without any ramifications? As you can see from Karl's review of this matter, my estimate of the situation was accurate and it appears as though the "high enroller in the entire 19 site SKB study" (me) was purposefully omitted from data review, analysis and publication. What do you suggest that I do at this point? I would appreciate your continued advice on this exceedingly troubling matter. I look forward to your suggestions at your convenience.

Best, as always,

Jay

Attachment O

X-Sender: krickels@mail.med.upenn.edu
X-Mailer: QUALCOMM Windows Eudora Pro Version 4.2.2
Date: Wed, 02 May 2001 11:23:55 -0400
To: jamsterd@mail.med.upenn.edu
From: "Dr. Karl Rickels" <krickels@mail.med.upenn.edu>
Subject: SKB study publication
Cc: "Dr. Dwight L. Evans, MD" <psych@mail.med.upenn.edu>

Dear Jay,

Dwight shared your email to him and asked me "to bring about a resolution". It would be helpful if you could let me know by email what steps you would like me or Dwight to take in this matter. After I receive your suggestions, I would be happy to come over to your office for any further clarification.

Best regards,

Karl
****

Karl Rickels, M.D.
Professor of Psychiatry
University of Pennsylvania
Department of Psychiatry
Mood and Anxiety Disorders Section
3535 Market Street
Suite 670
Philadelphia, PA 19104-3309

Telephone: 215-746-6417
Fax: 215-746-6551
email: krickels@mail.med.upenn.edu

Attachment P

To: Dr. Karl Rickels
From: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
Subject: SKB Paxil BP study publication
Cc:
Bcc:
Attached:

Dear Karl,

Thank you for your nice email in response to my note to Dr. Evans. I have given a great deal of thought as to how to resolve this extremely troubling matter. As per your investigation there is little doubt that these data were misappropriated from me and used and published without my knowledge and without regard to the significant contribution that I made to this study.

It is certainly not my intention to embarrass any of the authors who will eventually receive all the accolades when this paper comes to print. However, I am sure you will agree that there is little doubt that I was systematically slighted by Dr. Guylai. His statement to you that he contacted SKB about having my name included as an author does not, unfortunately, comport with what knowledgeable persons at SKB report.

I think that it is important to maintain the highest academic and collegial relationship at an institution such as Penn. Thus, the theft and publication of a professor's data by a junior faculty member should not go unnoticed and uncensured. Therefore, in an effort to assure that this situation does not happen again, I would propose the following:

1. Dr. Guylai write a letter of apology to me acknowledging his wrong doing and that he will not do this again in the future.

2. That Dr. Guylai receive a letter of censure from the chairman (copied to me) admonishing him not to engage in this sort of behavior in the future.

3. That Dr. Guylai receive a letter of censure from you, his section chief (copied to me) admonishing him not to engage in this sort of behavior in the future.

I think that this would resolve the immediate problem in a private, but useful, fashion; and will not result in any embarrassment to people who were uninvolved with the Penn site and unaware of Dr. Guylai's behavior. It will also serve as a warning that our academic freedom is paramount and should not be compromised by petty, personal vein glory.

I would be happy to discuss these suggestions with you at your convenience.

As ever,
Jay

Attachment Q

X-Sender: krickels@mail.med.upenn.edu
X-Mailer: QUALCOMM Windows Eudora Pro Version 4.2.2
Date: Mon, 21 May 2001 10:37:12 -0400
To: jamsterd@mail.med.upenn.edu
From: "Dr. Karl Rickels" <krickels@mail.med.upenn.edu>
Subject: SKB Publication
Cc: dlevans@mail.med.upenn.edu

Dear Jay,

I have shared your comments RE: SKB Publication, with Dr. Evans. Once I hear a response from him, I would like to get together with you on this topic.

Sincerely,
Karl
****

Karl Rickels, M.D.
Professor of Psychiatry
University of Pennsylvania
Department of Psychiatry
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3535 Market Street
Suite 670
Philadelphia, PA 19104-3309

Telephone: 215-746-6417
Fax: 215-746-6551
email: krickels@mail.med.upenn.edu

Attachment R

To: krickels@mail.med.upenn.edu
From: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
Subject: Am. J Psych paper
Cc:
Bcc:
Attached:

Dear Karl:

Months of inactivity and languishing over the issue of the upcoming SKB bipolar study, from which I have been excluded as a principal author, have produced no resolution (satisfactory or otherwise).

The article containing the data stolen from me has now appeared in print in the Am. J Psych 158: 906-912, 2001.

I suppose that the inactivity that I have seen indicates that I must now proceed at other levels regarding the "unacademic" and "un-collegial" behavior of Dr. Gyulai. Before I contact either University officials or the editorial board of Am J. Psych regarding this egregious behavior, I await your last efforts at resolution of this problem.

Jay

Attachment S

X-Sender: krickels@mail.med.upenn.edu
X-Mailer: QUALCOMM Windows Eudora Pro Version 4.2.2
Date: Wed, 13 Jun 2001 16:01:59 -0400
To: "Dr. Jay D. Amsterdam" <jamsterd@mail.med.upenn.edu>
From: "Dr. Karl Rickels" <krickels@mail.med.upenn.edu>
Subject: Re: Am. J Psych paper
Cc: "Dr. Dwight L. Evans, MD" <psych@mail.med.upenn.edu>

Dear Jay,

Sorry I have not responded earlier. Dr. Gyulai had a serious operation and is recuperating at home. I will definitely get back to you once Dr. Gyulai is returned to work.

Regards,

Karl

At 12:04 PM 6/13/01 -0400, you wrote:
Dear Karl:

Months of inactivity and languishing over the issue of the upcoming SKB bipolar study, from which I have been excluded as a principal author, have produced no resolution (satisfactory or otherwise).

The article containing the data stolen from me has now appeared in print in the Am. J Psych 158: 906-912, 2001.

I suppose that the inactivity that I have seen indicates that I must now proceed at other levels regarding the "unacademic" and "un-collegial" behavior of Dr. Gyulai. Before I contact either University officials or the editorial board of Am J. Psych regarding this egregious behavior, I await your last efforts at resolution of this problem.

Jay
Jay D. Amsterdam, M.D.
Depression Research Unit
3600 Market Street, 8th floor
Philadelphia, PA 19104-2649
ph 215.662.3462
fax 215.662.6443
email: jamsterd@mail.med.upenn.edu

****
Karl Rickels, M.D.
Professor of Psychiatry
University of Pennsylvania
Department of Psychiatry

Mood and Anxiety Disorders Section
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Philadelphia, PA 19104-3309

Telephone: 215-746-6417
Fax: 215-746-6551
email: krickels@mail.med.upenn.edu

Attachment T

UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER
University of Pennsylvania School of Medicine
Hospital of the University of Pennsylvania

Karl Rickels, M.D.
Stuart and Emily B. H. Mudd Professor
Chief, Mood and Anxiety Disorders Section
Department of Psychiatry

June 29, 2001

Jay D. Amsterdam, M.D.
Professor, Director,
Depression Research Unit,
Mood and Anxiety Disorders Section
Department of Psychiatry
University of Pennsylvania

RE: SKB PAR-29060/352

Dear Jay,

Laszlo Gyulai has now returned part-time from his sick leave, and I want to assure you that I will discuss this unfortunate situation with him today. I am sorry that this situation has developed this far, and I can assure you that the problem is of concern to me. I hope, sincerely, that this matter can be resolved between you and Laszlo in a collegiate matter.

Best regards,

Karl

Karl Rickels, M.D.

cc: Dwight L. Evans, M.D.
Laszlo Gyulai, M.D.

KR:tch

3535 Market Street • Suite 670 • Philadelphia, PA 19104-3309 • Tel: 215-746-6417 • Fax: 215-746-6551 • Email: krickels@mail.med.upenn.edu

Attachment U

e-mail sent 07/19/01

Dear Karl:

As you know, Dr. Gyulai sent me a letter on 7/05/01 regarding the SmithKline data and publication issue. I would like to inform you (as his Section Chief) that his letter is certainly NOT acceptable as an apology to me for his deliberate misappropriation and publication of my data. This matter was certainly NOT a "misunderstanding" on my part; nor was Dr. Gyulai the "primary investigator of the Penn site..." In fact, if Dr. Gyulai would simply read the Penn IRB-approved consent form for this study, he would clearly see that Dr. Amsterdam was listed as the "Co-Principal Investigator" on this study (not to mention the highest patient enroller in the study). Additionally, this study was NOT conducted at only one Penn site, but *was* conducted primarily from bipolar patients recruited from the *Depression Research Unit* under my direction! Finally, I have no idea of whether Dr. Gyulai ever wrote (or did not write) several drafts of the manuscript, or whether "the paper was taken away ..." from him, because Dr. Gyulai sequestered ALL available data and drafts of ALL manuscripts and NEVER communicated any information to me (the Co-PI) regarding any of these issues.

Thus, if you (as Dr. Gyulai's Section Chief) feel that his "apology" is sufficient to assuage this degree of uncollegial and unethical culpability in this matter, and neither you nor the Chairman feel that a letter of reprimand admonishing Dr. Gyulai NEVER to plagiarize a colleague's data ever again, is appropriate, then I will certainly take this troubling matter further.

Please feel free to comunicate your feelings to me regarding this issue in the *very near future* at your convenience.

Respectfully,

Jay

Attachment V

UNIVERSITY OF
PENNSYLVANIA
MEDICAL CENTER

University of Pennsylvania School of Medicine
Hospital of the University of Pennsylvania

Karl Rickels, M.D.
Stuart and Emily B. H. Mudd Professor

Chief, Mood and Anxiety Disorders Section
Department of Psychiatry

July 20, 2001

Jay Amsterdam, M.D.
Director Depression Research Unit
3535 Market Street, Suite 3039
Philadelphia, PA 19104

Dear Jay:

I am responding to your recent e-mail regarding the SmithKline bipolar paper. I trust you know that I really want to resolve this situation. As I indicated to you before, I regret that Dr. Gyulai did not discuss the issue of authorship of the paper with you.

I do want to indicate my understanding of how the study was conducted here at Penn. From my perspective, Dr. Gyulai was the principal investigator here at the Penn site. When it became clear that Dr. Gyulai was not recruiting at a rapid enough pace for the successful conduct of the study, I suggested that he discuss asking you to be involved with the study to increase the enrollment. From my memory, this occurred at a time when your program was in need of increased clinical trial activity and you were appropriately financially compensated for your work. I agree that you were very successful in recruiting subjects, but I do not believe Dr. Gyulai intended "deliberate misappropriation and publication" of data.

Again, I regret that Dr. Gyulai did not discuss the authorship with you, and as Dr. Gyulai's Program Director, I made this very clear to him.

I also agree that it is unfortunate that Smith-Kline Beecham did not circulate the manuscript to you and I regret that Dr. Gyulai did not share it with you. Once again, as Dr. Gyulai's Program Director, I have expressed my belief that he should have done so.

I would be happy to sit and discuss this with you further, and I would be happy to involve Dr. Gyulai in this discussion with you if you'd like.

Sincerely,

Karl Rickels, M.D.

cc: Dwight L. Evans, M.D.
Laszlo Gyulai, M.D.

3535 Market Street • Suite 670 • Philadelphia, PA 19104-3309 • Tel: 215-746-6417 • Fax: 215-746-6551 • Email: krickels@mail.med.upenn.edu

Attachment W

From: Sally Laden <sally.laden@cox.net>

To: eric.m.dube@gsk.com

Subject: Proposal for 2 review articles

Date: 07/28/2003 09:40:30 (GMT-05:00)

Dear Eric:

Thank you for thinking of me for the Safety in Breast Feeding and the Tolerability of PaxilCR review articles. A proposal for both is attached. Please review and contact me with questions. As we discussed on Friday, I am not able to start work on these papers until September, but if we decide to move forward, I will reserve that month for these projects.

Two other questions:

1) Lydia Lewisfrom the DBSA asked me to be the writer for their upcoming dual diagnosis consensus meeting this November. She mentioned that Scott committed GSK to funding the writing costs for the consensus statement. Lydiais asking if GSK will be able to paying me directly rather than offering the DBSA a grant for the cost of the writing. I am having problems connecting with Scott. If you see him in the near future, would you inquire about this? I would submit the proposal directly to GSK and bill GSK directly. (Thanks)

2) Is there a problem with my invoice for writing Dwight Evans , editorial for the DBSA ,scomorbidity issue to Biological Psychiatry? I submitted it over a month ago and was wondering about the status. If the payment cycle >30 days, so be it. I was just wondering.

Thanks again Eric. I look forward to working with you again.

Sally Laden MSE Communications

898 Cahill Court Cheshire, CT06410

T 203 y271-1047 F 203 y271-1054 E sally.laden@cox.net

- New business proposals.doc

Attachments: New business proposals.doc;embedded picture.bmp

PAR070321650

Attachment X

EDITORIAL

Mood Disorders and Medical Illness: A Major Public Health Problem

Despite efficacious and widely available antidepressants and psychotherapeutic interventions, the psychosocial and medical burden of depression is increasing. In fact, the World Health Organization projects that depression will continue to be prevalent, and by the year 2020, will remain a leading cause of disability, second only to cardiovascular disease (Michaud et al 2001). Although we do not know with certainty why rates and disability associated with depression are increasing, it is likely that this mood disorder continues to be remarkably under-recognized and under-treated. Depression frequently occurs in the context of chronic medical illness, and it is only relatively recently that the research community has turned its attention to the relationship between depression and chronic medical conditions. However, there is much work yet to be done. The recently released Institute of Medicine report (2003) acknowledged depression as one of a number of chronic conditions that requires priority action, but did not address the importance of comorbid depression and medical illness.

The relationship between depression and medical illnesses is complex. A chronically ill patient who also is clinically depressed may experience enhanced morbidity, a poorer prognosis, and even increased mortality from the medical diagnosis. Simply put, depression makes everything worse. But the association with depression goes beyond the effects of comorbidity on the course and outcome of a medical illness. A burgeoning body of evidence has now demonstrated that the relationship between depression and certain medical illnesses may indeed be bidirectional in nature. Depression may be both a cause and a consequence of some medical illnesses, such as cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy.

In recognition of the need to increase awareness about this topic and improve the quality of life for persons with depression, the Depression and Bipolar Support Alliance, the world's largest patient advocacy organization, convened a two-day, multidisciplinary consensus conference on November 12, 2002 in Washington, DC. Nearly 50 experts in the fields of psychiatry, cardiology, immunology, oncology, neurology, endocrinology, internal medicine, family medicine, federal health care agency policy and research, and patient advocacy participated in this process. Formal presentations centered around the perspectives and goals of the National Institutes of Health and the Food and Drug Administration, the personal and societal burden of depression and medical illness, and the epidemiology, mechanisms, diagnosis, treatment, and prognosis of depression in the context of cardiovascular disease, cancer, HIV/AIDS, stroke, neurologic diseases, diabetes, osteoporosis, obesity, and chronic pain. Workgroups met to discuss specific issues related to these topics and on the second day, workgroup leaders presented their findings and facilitated open discussions from the group.

Burden of Mood Disorders and Medical Illness

The functional impairment associated with depression contributes significantly to the economic burden of chronic medical illness. Depression also is becoming recognized as a cause of increased morbidity and mortality in chronic medical illness. As reviewed by Katon (2003), medical costs for patients with major depression are approximately 50% higher than the costs of chronic medical illness alone. In addition, Katon (2003) underscores the equally important, but often less appreciated, effects of depression on adverse health behaviors, such as smoking, unhealthy diet, sedentary lifestyle, and poor adherence to medical regimens (e.g., cardiac rehabilitation). The findings from a number of studies have established that major depression is associated with significant functional impairment, lost work productivity, occupational disability, and increased health care resource utilization, and that effective treatment restores functioning. Simon (2003) reviews these data in the context of evidence from recent cross-sectional, longitudinal, and treatment studies of depressed patients with and without arthritis, chronic obstructive pulmonary disease, diabetes, or heart disease. This emerging body of evidence demonstrates that depression significantly increases the burden of functional impairment in medical illness, and that treatment reduces disability and health service costs. The effect of other mood disorders, such as dysthymia or bipolar disorder, on the burden of chronic medical illness is remarkably understudied.

Cardiovascular Disease

It is now recognized that major depression and bipolar disorder are associated with increased rates of death from

0006-3223/03/$30.00
doi:10.1016/S0006-3223(03)00639-5

coronary heart disease (CHD), and that major depression or depressive symptoms increase the risk of incident CHD (Musselman et al 1998). As reviewed by Rudisch and Nemeroff (2003), as many as 27% of patients with CHD have major depression, but a substantially larger number of cardiac patients have subsyndromal depressive symptoms. Depression is a particularly lethal development for patients with acute myocardial infarction (MI). In the United States, there are approximately 150,000 deaths in the first year after an initial MI, and Carney and Freedland (2003) estimate that at least 90,000 of these deaths may be related to post-MI depression. The cumulative body of evidence in support of an association between depression and cardiovascular disease is large and impressive; Carney and Freedland (2003) evaluate this literature and outline future directions for research, including studies that will better elucidate the role of depression in the development and progression of atherosclerosis, ischemia, and arrhythmias.

One particularly diverse and robust field of research is dedicated to better understanding the mechanisms that underlie the relationship between depression and cardiovascular disease. In their paper, Joynt and colleagues (2003) overview seven probable mechanisms associated with depression that may be related to cardiovascular disease: noncompliance with cardiac rehabilitation and medical regimens; risk factor clustering (e.g., smoking, hypertension, diabetes, hypercholesterolemia, obesity); hypothalamic-pituitary-adrenal (HPA) axis hyperactivity and cortisol elevation; decreased heart rate variability; elevated plasma levels of pro-inflammatory cytokines leading to atherosclerosis; platelet activation and hypercoagulability; and psychological stress.

The demonstrated adverse effect of depression on the risk of new and progression of established CHD has spurred the next emergent area of clinical study in this field: the consequences of depression treatment on cardiovascular morbidity and survival. As noted in the paper by Roose (2003), findings from the few open-label or randomized, controlled clinical trials suggest that the selective serotonin reuptake inhibitors (SSRIs), bupropion, and certain psychotherapeutic interventions are safe and effective treatment of depression in patients with CHD. The tricyclic antidepressants (TCAs) increase heart rate, cause orthostatic hypotension and conduction delays, have been shown to increase the risk of cardiac mortality, and should be avoided in this patient population. There is one published placebo-controlled trial, which suggests that SSRI treatment of depressed post-MI patients may improve outcome and increase survival, but this study was not adequately powered to find significant changes in these cardiac disease outcomes. Thus, it is still not known whether treatment of depression enhances the outcome of the cardiac disease. Further study is clearly needed.

Cancer

As with cardiovascular disease, there is a large and growing body of evidence in support of a relationship between depression and cancer. Research efforts have focused on depression as a risk factor for cancer, depression as a consequence of cancer, and the dynamics of comorbid depression and cancer. Large population studies suggest that depressed mood or stressful life events may increase the risk of cancer. Although it is acknowledged that these observations of increased risk may be due in part to earlier, undetected malignancies or factors other than depression (Lillberg et al 2003; Penninx et al 1998), these findings are compelling and further study is warranted.

Depression also is a common occurrence in patients with a wide range of different malignancies and often prevents patients from complying with treatment regimens and other health-promoting behaviors, thus worsening the prognosis. A diagnosis of cancer represents a significant life stressor, which in vulnerable persons can precipitate an episode of depression. In addition, patients with cancer may develop "sickness behavior" or depressive syndromes due to proinflammatory cytokine activation that is the result of tumor cell burden, tissue destruction, radiation treatments, and chemotherapy. The papers by Raison and Miller (2003) and Spiegel and Giese-Davis (2003) review the relationships between depression and cancer and offer insight into disease progression and treatment. Of immediate clinical utility are the findings of studies showing that pretreatment with serotonergic antidepressants can prevent neurotoxicity and clinical depression in patients treated with interferon-alpha.

HIV/AIDS

Mood disorders, including depression and mania, are prevalent in persons with human immunodeficiency virus (HIV) disease and may be associated with impaired quality of life, neurocognitive and functional impairment, and poor adherence to antiretroviral therapy. In addition, emerging data suggest that depression is associated with declining CD4 cell counts, accelerated disease progression, and increased mortality. In their paper, Cruess and colleagues (2003) discuss the negative impact of mood disorders on HIV/AIDS and review evidence for safety and efficacy of antidepressants, mood stabilizers, and novel pharmacotherapies in this population (Evans et al 2002a). Leserman (2003) also reviews this topic, but with a focus on the biological mechanisms underlying the relationship between mood disorders and HIV disease

and the immune effects that result from this comorbidity (Leserman et al 1997; Evans et al 2002b). Patients with HIV/AIDS and comorbid depression are a significantly underserved and understudied population. Further epidemiologic, biological, and therapeutic studies are urgently needed to better understand the nature of this comorbidity, increase case-finding, and develop effective treatment strategies.

Neurologic Disease

This special issue also includes papers devoted to the topics of depression and comorbid neurologic disorders, such as stroke, Parkinson's disease, Alzheimer's disease, and epilepsy. Of these neurologic disorders, the relationship between mood disorders and cerebrovascular accidents is particularly well-studied. As reviewed by Robinson (2003), depression is common in poststroke patients, with reported prevalence rates of approximately 20%; bipolar disorder is less common. There is no standardized diagnostic approach for poststroke depression, and the controversies surrounding various approaches are summarized by Robinson (2003). The findings of treatment studies showing efficacy of antidepressants, electroconvulsive therapy, psychostimulants, and cognitive behavioral therapy in patients with poststroke depression are of considerable clinical importance. Importantly, treatment of depression improves measures of function and cognition and may result in improved survival. Evidence that antidepressants may prevent poststroke depression offers hope. As with many other medical comorbidities, depression may increase the risk of stroke, and the findings of two large epidemiologic studies support the role of depression as a risk factor for stroke. These findings further underscore the importance of identifying the underlying biological mechanisms associated with depression comorbidity.

Depression occurs in roughly half of patients with Parkinson's disease and is associated with significant impairment, including reduction in fine motor skills and cognitive function. In their paper, McDonald and colleagues (2003) review the distinct presentation of depression in this population, discuss the challenges associated with diagnosis, and highlight the need for more sensitive screening and diagnostic tools.

Depression in this population may not be due simply to the disability and added life stressors associated with Parkinson's disease. Rather, emerging evidence suggests that depression in these patients may be a consequence of neurodegeneration. Treatment of depression in Parkinson's disease is complicated by variable responses, sensitivity to adverse effects, and drug interactions. Randomized, placebo-controlled trials, particularly of the SSRIs and dopamine agents, are needed. The findings of functional neuroimaging studies are presented, which may eventually lead to the improved understanding of the neurocircuitry of depression in Parkinson's disease.

Even though depression occurs in as many as 50% of patients with Alzheimer's disease, contributing to accelerated functional and cognitive decline, impaired quality of life, care-giver depression, and earlier institutionalization, surprisingly little evidence-based data are available to inform diagnosis and treatment. The diagnosis of depression in this cohort is particularly challenging because symptoms, such as psychomotor retardation, insomnia, and emotional liability, which occur in nondepressed patients with Alzheimer's disease may be difficult to differentiate from a true depressive episode. Moreover, symptoms of dementia may mask an underlying depressive disorder. In an effort to guide research and better inform clinical care, the National Institute of Mental Health has undertaken the task of developing diagnostic criteria for depression in Alzheimer's disease. Lee and Lyketsos (2003) review these developments and describe an ongoing longitudinal study of depression and other neuropsychiatric comorbidities in new cases of Alzheimer's disease, which will provide valuable information on the epidemiology, natural course, and diagnosis of depression in this population.

Epilepsy is another neurologic disorder that often is complicated by comorbid depression. As many as 50% of epileptic patients seen in tertiary treatment centers may have depression, and suicidality among depressed epileptics have been reported to be as high as 10 times the rate than in the general population. Kanner (2003) reviews the challenges related to diagnosing depression in epilepsy: patients often present with atypical depressive symptoms (e.g., anxiety, irritability, hypomania, pain); the peri-ictal period often is associated with a recurrent and short-lived dysphoria that is clinically significant but does not conform to standard diagnostic criteria; and antiepileptic drugs and surgical intervention can be iatrogenic causes of depression. Clearly, epilepsy is a risk factor for depression; however, recent evidence suggests that depression may increase the risk for epilepsy by 4- to 6-fold. Further studies are needed to better characterize this complex relationship.

Call for Action

The contributions made by this conference and the papers published in this special issue of *Biological Psychiatry* should not simply be measured by the quality and quantity of the data, which are impressive. Rather, the strength of this publication also lies in the fact that the views of experts from widely divergent fields of clinical and scien-

tific endeavor resonate along 4 basic themes: 1) Depression is very common in chronic medical illness; 2) Comorbidity with depression inevitably hinders recovery and worsens prognosis; 3) Medical illness is a risk factor for depression because of psychosocial stressors, functional impairment, and other biological mechanisms (e.g., Parkinson's disease); and 4) Depression may figure prominently as an etiologic factor in the onset and course of medical illness, particularly cardiovascular disease, stroke, HIV/AIDS, cancer, and epilepsy. The latter observation is truly remarkable. Much more research is needed to better understand this bidirectional relationship and identify possible common pathogenic, mechanistic pathways that link depression and serious medical illness.

These are powerful messages that must not be ignored. The weight of evidence is so persuasive that there should never again be a valid reason for not aggressively seeking out and treating depression in medically ill patients. Increasing awareness, reducing stigma, and maintaining a high level of vigilance for depression in medically ill patients must become a priority for clinicians. In addition, the efforts of the research communities must continue to better elucidate the prevalence, risk profile, diagnostic criteria, treatment, and biological underpinnings of the comorbid relationship between depression and medical illness. Only by furthering research efforts and aggressively diagnosing and treating depression, will we be able to achieve substantive gains in health care and in our patients' quality of life.

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References

Carney RM, Freedland KE (2003): Depression, mortality, and medical morbidity in patients with coronary heart disease. *Biol Psychiatry* 54:241–247.

Cruess DG, Evans DL, Repetto MJ, Gettes D, Douglas SD, Petitto JM (2003): Prevalence, diagnosis, and pharmacological treatment of mood disorders in HIV disease. *Biol Psychiatry* 54:307–316.

Evans DL, Mason K, Bauer R, Leserman J, Petitto J (2002a): Neuropsychiatry manifestations of HIV-1 Infection and AIDS. In: Charney D, Coyle J, Davis K, Nemeroff C, editors. *Neuropsychopharmacology: The Fifth Generation of Progress*. New York, NY: Raven Press, 1281–1300.

Evans DL, Ten Have TR, Douglas SD, Gettes DR, Morrison M, Chiappini MS, et al (2002b): Association of depression with viral load, CD8 T lymphocytes, and natural killer cells in women with HIV infection. *Am J Psychiatry* 159:1752–1759.

Institute of Medicine (2003): *Priority Areas for National Action: Transforming Health Care Quality*. In: Adams K, Corrigan JM, editors. Washington, DC: The National Academies Press.

Joynt KE, Whellan DJ, O'Connor CM (2003): Depression and cardiovascular disease: Mechanisms of interaction. *Biol Psychiatry* 54:248–261.

Kanner AM (2003): Depression in epilepsy: Prevalence, clinical semiology, pathogenic mechanisms, and treatment. *Biol Psychiatry* 54:388–398.

Lee HB, Lyketsos CG (2003): Depression in Alzheimer's disease: Heterogeneity and related issues. *Biol Psychiatry* 54: 353–362.

Leserman J (2003): HIV disease progression: Depression, stress, and possible mechanisms. *Biol Psychiatry* 54:295–306.

Leserman J, Petitto JM, Perkins DO, Folds JD, Golden RN, Evans DL (1997): Severe stress, depressive symptoms, and changes in lymphocyte subsets in human immunodeficiency virus-infected men: A 2-year follow-up study. *Arch Gen Psychiatry* 54:279–285.

Lillberg K, Verkasalo PK, Kaprio J, Teppo L, Helenius H, Koskenvuo M (2003): Stressful life events and risk of breast cancer in 10,808 women: A cohort study. *Am J Epidemiol* 157:415–423.

Katon WJ (2003): Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. *Biol Psychiatry* 54:216–226.

Michaud CM, Murray CJ, Bloom BR (2001): Burden of disease: Implications for future research. *JAMA* 285:535–539.

McDonald WM, Richard IH, DeLong MR (2003): The prevalence, etiology, and treatment of depression in Parkinson's disease. *Biol Psychiatry* 54:363–375.

Musselman DL, Evans DL, Nemeroff CB (1998): The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. *Arch Gen Psychiatry* 55:580–592.

Penninx BW, Guralnik JM, Pahor M, Ferrucci L, Cerhan JR, Wallace RB, et al (1998): Chronically depressed mood and cancer risk in older persons. *J Natl Cancer Inst* 90:1888–1893.

Raison CL, Miller AH (2003): Depression in cancer: New developments regarding diagnosis and treatment. *Biol Psychiatry* 54:283–294.

Robinson RG (2003): Poststroke depression: Prevalence, diagnosis, treatment, and disease progression. *Biol Psychiatry* 54:376–387.

Roose SP (2003): Treatment of depression in patients with heart disease. *Biol Psychiatry* 54:262–268.

Rudisch B, Nemeroff CB (2003): The epidemiology of comorbid coronary artery disease and depression. *Biol Psychiatry* 54: 227–240.

Simon GE (2003): Social and economic burden of mood disorders. *Biol Psychiatry* 54:208–215.

Spiegel D, Giese-Davis J (2003): Depression and cancer: Mechanisms and disease progression. *Biol Psychiatry* 54:269–282.